American Heart Journal

An international publication for the study of the circulation

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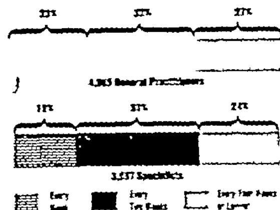
Current Role of the Prothrombin Time Test In Regulating Anticoagulant Therapy

Anticoagulant therapy can be no better than its laboratory control.[1] Regular prothrombin time testing by trained technical personnel provides an objective index to individualized therapeutic anticoagulation with a minimum of complications. Since dependable facilities and reliable technicians are now available to most physicians, the growing number of ambulatory patients who require anticoagulant therapy can be managed successfully in both specialty and general practice.

Endo Laboratories *Anticoagulant Survey* covering the practices of 10,016 physicians across the nation, provides answers to such questions as the *frequency of prothrombin time tests* and the *preferred therapeutic prothrombin time range* at which the ambulatory nonhospitalized patient is maintained.

Tests Generally Spaced at Intervals of Two Weeks or Longer

According to *Anticoagulant Survey*, the predominant trend is toward performing prothrombin time tests at intervals of *two weeks or longer*.



Frequency of Prothrombin Time Tests

The spacing of tests at longer intervals is more common among the 5,718 physicians using Coumadin,[*] the most widely prescribed oral anticoagulant, than among the 2,493 physicians employing Dicumarol.[*]

Physicians Favor Therapeutic Prothrombin Time At Twice Normal Level

A total of 9,0?4 physicians replied to the question *At what prothrombin level do you prefer to maintain your ambulatory nonhospitalized patients?* The therapeutic prothrombin time preferred by most general practitioners and specialists is 2 x the normal control time. The following table shows the prothrombin time levels established and maintained by respondents regardless of the oral anticoagulant administered.

Times Normal Control	Percentage of Responding Physicians
1½	25%
2	47%
2½	25%
3	3%

Preferred Prothrombin Time Levels

Prothrombin Time Tests Monitor Safety and Efficacy Of Treatment

The Quick one-stage prothrombin time test is a highly reproducible, relatively simple procedure that continues to provide a reliable gauge of the safety and efficacy of anticoagulant control.[2,3] The findings of *Anticoagulant Survey* relating to preferred prothrombin time are confirmed in the literature: the optimal therapeutic level in a given patient is usually found to be 1½ to 2½ times the control level.[2-5] For greater uniformity and precision, reporting in *seconds* in addition to, or in place of, *percentage prothrombin activity* has been strongly advocated.[4]

With Coumadin, the "predictability of action and desirable character of the response" are especially favorable to the ease of maintenance of a therapeutic hypoprothrombinemic range. Experience in long-term treatment of office patients has demonstrated that "once an individual was stabilized, the dose remained quite fixed and the prothrombin time remained at a constant level. . . ."[6] The clinically established warfarin sodium, Coumadin is available in the widest range of dosage forms, permitting precise individualization of treatment in both hospital and office practice.

1. [illegible] 2. [illegible] 3. [illegible] 4. [illegible] 5. [illegible] 6. [illegible]

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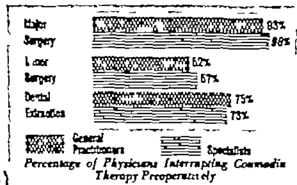
No. 7 *of a series reporting on Endo Laboratories' Anticoagulant Survey*

Current Use of Anticoagulants in the Surgical Patient

The question of *modifying* established anticoagulant dosage schedules of patients about to undergo surgery or of *initiating* anticoagulant therapy in postoperative patients has become increasingly important. This has resulted from the wider use and appreciation of the value of anticoagulants in thromboembolic disorders. The responses of the 10 016 physicians who participated in Endo Laboratories nationwide *Anticoagulant Survey* provide a broad base of experience which permit evaluation of their customs relating to pre- and postoperative administration of anticoagulants

Before Surgical Procedures

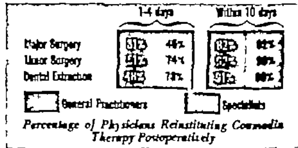
The following data from the *Survey* show the extent to which responding physicians interrupt therapy with Coumadin—the most frequently prescribed oral anticoagulant—before major surgery before minor surgery and before dental extraction.



Percentage of Physicians Interrupting Coumadin Therapy Preoperatively

After Surgical Procedures

Anticoagulant Survey data indicate that once surgery is completed, specialists reinstitute Coumadin therapy *earlier* than do general practitioners.



Percentage of Physicians Reinstituting Coumadin Therapy Postoperatively

The great majority of responding physicians in the 1-4 day group resume anticoagulant therapy on the *second* or *third* postoperative day In the other group, most physicians reinstitute treatment on the *seventh* postoperative day

Recent Clinical Experience

The protective value of anticoagulant therapy must be weighed against the risk of hemorrhage in each surgical patient. Determining factors include the type of surgery the age and physical status of the patient, any known bleeding or clotting tendencies, and the characteristics of the anticoagulant itself. It is generally agreed that anticoagulation appreciably lessens the risk of postoperative thromboembolism.[1-4] For example, in the surgical correction of mitral stenosis, patients under anticoagulant control have shown significantly fewer fatal systemic emboli.[3] Alexander and Wessler[5] recommend discontinuation of *anticoagulant drug administration before major* or minor surgery until the prothrombin activity has returned to a level above 30 per cent. They recommend further that anticoagulant therapy be then resumed, with certain exceptions, *on the day of surgery* until therapeutic hypoprothrombinemic levels are once again established. These authors note that some investigators indicate that minor procedures however can be performed safely with the prothrombin time in the therapeutic range.

Citing successful amputation, venous ligation, lumbar sympathectomy and even lobectomy *without* interruption of anticoagulant medication, Behrman and Wright[1] report that when the prothrombin time is adjusted to a low optimal range, "anticoagulants need not be discontinued for appropriate dental surgery" and observe that abrupt discontinuance may be dangerous. Belding[4] has commented on the outstanding *constancy* and *predictability* of response to Coumadin given postoperatively and has noted "no instances of wound hemorrhage"

1 Behrman, S. J. and Wright, I. S. J.A.M.A. [illegible] 1961 2 [illegible] 3 [illegible] 4 Belding, H. H. [illegible] 5 Alexander, B. and Wessler, S. [illegible] 1961

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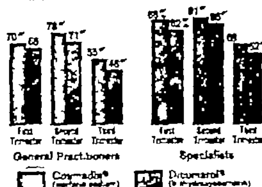
8 of a series reporting on Endo Laboratories Anticoagulant Survey

Current Use of Anticoagulants in the Obstetrical Patient

The principal objectives of anticoagulation in the obstetrical patient with thromboembolic disease are to prevent pulmonary embolism and to minimize other thrombophlebitic sequelae. Endo Laboratories' *Anticoagulant Survey* has reviewed the antepartum and postpartum use of anticoagulant therapy by 10,016 responding physicians across the nation.

Anticoagulants Now Widely Prescribed During Pregnancy

According to the *Survey* data physicians will usually administer an anticoagulant to a pregnant patient when there is *sufficient indication* for its use. Among the 3,092 general practitioners and 2,626 specialists preferring Coumadin® the most widely prescribed oral anticoagulant, *and the 1,689 general practitioners and 801* specialists using Dicumarol® anticoagulant therapy is extensively employed during the first and second trimesters but to a significantly *lesser degree during the third trimester of pregnancy* because of the necessity of minimizing hemorrhagic tendencies before and during delivery. From 91 to 93 per cent of physicians *interrupt treatment before delivery. The following* data indicate that *specialists* lead in prescribing anticoagulants in every trimester.



Percentage of Physicians Prescribing Anticoagulant Therapy in Each Trimester of Pregnancy

Anticoagulation Resumed Soon After Delivery

Anticoagulant Survey data show that anticoagulant schedules interrupted prior to delivery are soon restored in the postpartum period. Specialists appear more disposed than general practitioners to resume therapy within 1-4 days after delivery, usually on the *second* or *third* postpartum day. Most general practitioners, however, reinstitute anticoagulation by the *seventh* postpartum day.

Maternal Safety Primary Consideration

Since thromboembolic disease in the obstetrical patient, as in any other, can lead to pulmonary embolism which may be fatal, *considerations of maternal well-being largely determine* the ante- and postpartum use of anticoagulant therapy. Anticoagulants have been effectively employed during pregnancy in thrombotic *disorders affecting surface or deep veins*[1-4] *and in* the rare cases of myocardial infarction[1] with a remarkable lack of complications and recurrences of the disease processes. *Although fetal damage has sometimes been reported, most* clinicians believe that antenatal use of anticoagulants to treat thromboembolic disease is justified provided that proper control is exercised.[2] *In summary, anticoagulation during* pregnancy[3,4,5] and also after delivery[3,4] has proved itself a highly beneficial therapeutic and prophylactic measure for prevention and treat*ment of thromboembolic disease.*

Coumadin is especially suited to the anticoagulant management of the obstetrical patient because of its notable *promptness of action* and *ease of control*. With an unparalleled background of clinical use, Coumadin offers the widest range of dosage forms for precise individualization of treatment in hospital and office practice.

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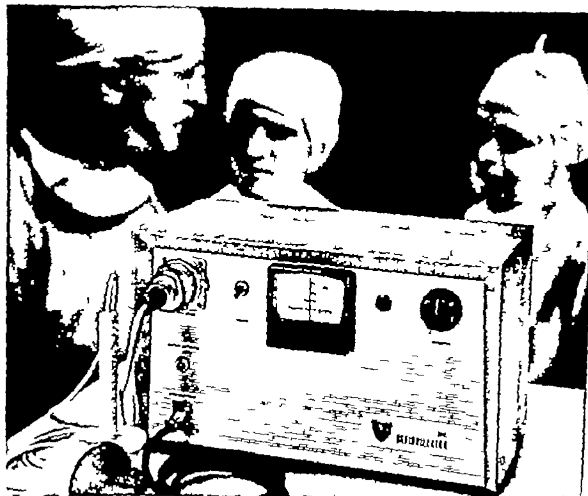
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8 of a series reporting on Endo Laboratories' Anticoagulant Survey

Current Use of Anticoagulants in the Obstetrical Patient

The principal objectives of anticoagulation in the obstetrical patient with thromboembolic disease are to prevent pulmonary embolism and to minimize other thrombophlebitic sequelae. Endo Laboratories' *Anticoagulant Survey* has reviewed the antepartum and postpartum use of anticoagulant therapy by 10 016 responding physicians across the nation.

Anticoagulants Now Widely Prescribed During Pregnancy

According to the *Survey* data, physicians will usually administer an anticoagulant to a pregnant patient when there is sufficient indication for its use. Among the 3,092 general practitioners and 2,626 specialists preferring Coumadin® the most widely prescribed oral anticoagulant, and the 1,689 *general practitioners* and 804 specialists using Dicumarol® anticoagulant therapy is extensively employed during the first and second trimesters but to a significantly lesser degree during the third trimester of pregnancy because of the necessity of minimizing hemorrhagic tendencies before and during delivery From 91 to 93 per cent of physicians interrupt treatment before delivery The following data indicate that *specialists* lead in pre[illegible] anticoagulants in every trimester

Percentage of Physicians Prescribing Anticoagulant Therapy in Each Trimester of Pregnancy

Anticoagulation Resumed Soon After Delivery

Anticoagulant Survey data show that anticoagulant schedules interrupted prior to delivery are soon restored in the postpartum period. Specialists appear more disposed than general practitioners to resume therapy within 1-4 days after delivery usually on the *second* or *third* postpartum day Most general practitioners, however reinstitute anticoagulation by the seventh postpartum day

Maternal Safety Primary Consideration

Since thromboembolic disease in the obstetrical patient, as in any other can lead to pulmonary embolism which may be fatal, considerations of maternal well-being largely determine the ante and postpartum use of anticoagulant therapy Anticoagulants have been effectively employed during pregnancy in thrombotic disorders *affecting surface or deep veins*[1-4] *and in* the rare cases of myocardial infarction[5] with a remarkable lack of complications and recurrences of the disease processes. Although fetal damage has sometimes been reported, most clinicians believe that antenatal use of anticoagulants to treat thromboembolic disease is justified provided that proper control is exercised.[2] In summary anticoagulation during pregnancy[1-4] and also after delivery[1,6] has proved itself a highly beneficial therapeutic and prophylactic measure for prevention and treatment of thromboembolic disease.

Coumadin is especially suited to the anticoagulant management of the obstetrical patient because of its notable *promptness of action* and *ease of control.* With an unparalleled background of clinical use, Coumadin offers the widest range of dosage forms for precise individualization of treatment in hospital and office practice.

[illegible] Current Therapy—[illegible] Philadelphia, Saunders, [illegible] 3. McCarthy [illegible] 5. Nelson, R. S., Jr. et al. J.A.M.A. [illegible]

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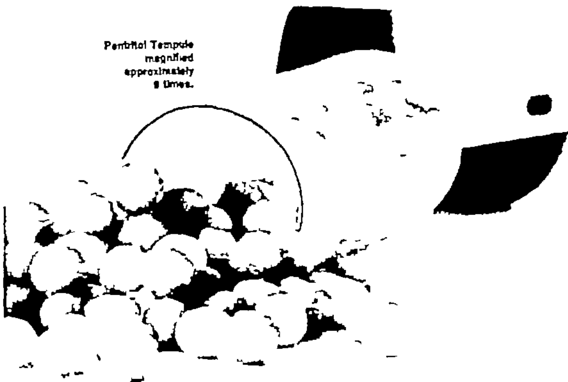
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American Heart Journal

January 1962 Volume 63 Number 1

Editorial

Selected clues in cardiac auscultation

John H Phillips Jr M.D
George E. Burck M.D
New Orleans La

Elaborate apparatus unfortunately at times tends to supersede thought and sound clinical medicine. The neglect of physical diagnosis at the bedside for the more ultimate" means of diagnosis may be the result This applies in cardiac auscultation To the discerning clinician however laboratory procedures which include cardiac catheterization phonocardiography angiocardiography and the like can help advance physical diagnosis. For example they may provide a clearer understanding of auscultatory phenomena. Although understanding may result from elaborate means a defect still remains in the practical application of knowledge gained by these means. This is due in large part to relatively inadequate reporting of data, much of which are not obtained or studied by able clinicians. Thus emphasis on factors of practical value in physical diagnosis is frequently inadequate. The purpose of this presentation is to indicate selected useful auscultatory procedures and clinical auscultatory tricks which are helpful at the bedside

The stethoscope should be provided with both the bell" and the diaphragm" types of chest piece. The earpieces should fit comfortably and snugly The tubing should be of stiff rubber fairly thick walled with an internal diameter of about 1/8 inch and a length of about 10 inches or less [1,2] Leaks, loose connections, cracked diaphragms or other sources of noises should be corrected The common practice of substituting x-ray film for the diaphragm supplied by the manufacturer is not advised

The diaphragm of the stethoscope is designed to filter out sounds of low frequency and thus is most useful in detecting high-pitched murmurs such as those of aortic and pulmonic insufficiency The bell tends to filter out sounds of high frequency and accentuate those of low frequency Contrary to common thought the bell of the stethoscope should not be considered a simple collector of sound When the bell is applied to the skin of the chest wall the skin becomes a "diaphragm with varying natural vibratory frequency characteristics depending upon the pressure applied thus making it well suited for transmission of sounds and noises of low and high frequency or pitch. With light pressure the bell is best suited for detecting murmurs of low frequency such as mitral and tricuspid rumbles. Thus the examiner may utilize a system of "built in filters during his examination. For example the firmer the bell is pressed against

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the chest wall the more tense the area of the underlying skin or dermal diaphragm becomes. When the skin is stretched tight by firm pressure the transmission of high pitched sounds is favored low-pitched ones are filtered-out With quite firm pressure the transmission characteristics of the bell approach those of the regular stethoscope diaphragm By varying or lessening the pressure which is applied the frequency level of the transmitted sounds tends to be varied These features are particularly useful in detecting soft low-pitched diastolic murmurs such as the Carey Coombs murmur

For thorough auscultation one should listen to the heart when the patient is sitting erect, sitting and leaning forward lying supine, and lying in the partial left lateral decubitus position This should be done during normal respiration during deep inspiration and deep expiration and during a deeply held inspiration and expiration Soft basal diastolic blows of aortic or pulmonic insufficiency are frequently heard only during auscultation when the patient is sitting up and leaning forward during a forced held expiration Occasionally these murmurs may be heard only when the patient is lying prone supported on his elbows during a forced held expiration A faint diastolic rumbling murmur of mitral stenosis frequently may be heard in a sharply localized point and only with the patient in a partial left lateral decubitus position and occasionally only during the actual act of rolling into this position

In addition to their timing location transmission and associated features, the fine quality or character of the murmurs may be helpful in difficult cases in localizing their site of origin One has no difficulty in differentiating the diastolic "rumbles" of mitral or tricuspid stenosis from the diastolic "blows" of aortic or pulmonic insufficiency Without careful examination however the systolic murmurs at times may not be so clearly different in quality The confusion of mitral insufficiency with aortic stenosis when the murmur of the latter is loudest at the apex is well known Systolic murmurs may be of two types[4] Ejection murmurs are those for example which arise at the aortic or pulmonic valves when either forward flow is increased the valve narrowed or the vessels beyond dilated They tend to be "diamond shaped" start after the first sound and cease before the second sound Regurgitant murmurs are those for example which result from backward flow of blood through incompetent mitral or tricuspid valves. They are pansystolic and extend from the start of the first sound to through and often slightly beyond the second sound They are typically not "diamond-shaped" and tend to be equally loud throughout systole or with a slight late systolic crescendo

A knowledge of the influence of respiration on circulatory dynamics can be helpful in auscultation at the bedside Briefly during inspiration the diaphragm descends and the intra abdominal *pressure increases* whereas the expanding thorax and descending diaphragm reduce intrathoracic pressure This has the effect of "pushing" and "sucking" blood into the right side of the heart With respect to the left side of the heart during inspiration the vascular capacity of the pulmonary bed is increased more blood is accommodated and thus there tends to be relatively less volume flow to the left side of the heart During expiration reverse events tend to take place on both the right and the left sides of the heart

It is diagnostically useful to study the splitting of the second heart sound at the pulmonic area or below it[2-4] True splitting of the heart sounds is due to asynchronous closure of valves. In the pulmonic area it is due to asynchronous closure of the aortic and pulmonic valves. Normally the aortic valve closes first and the pul

of the pulmonic valve occurs earlier and tends to coincide with closure of the aortic valve and thus produces a single second sound or minimal splitting. Generally, it is the pulmonic, not the aortic, component of the second heart sound that moves phasically with respiration.

Thus any procedure which tends to produce asynchronous closure of the aortic or pulmonic valves may produce splitting of the heart sounds. Splitting might be produced by electrical or mechanical cardiac phenomena. The *electrical causes* include bundle branch block, premature ventricular contractions, and idioventricular rhythm, all of which cause asynchronous activation of the two ventricles and associated asynchrony in closure of the valves. The *mechanical causes* may be as follows: (1) that which occurs normally with respiration due to phasic changes in ventricular emptying times as cited above; (2) any factor which might tend to accentuate intrathoracic negative pressure on inspiration, such as airway obstruction or decreased pulmonary compliance; (3) shunts which tend to cause differences in volume loads of the two ventricles, e.g., as in atrial septal defect; (4) leak offs which tend to decrease ventricular emptying time, e.g., as in mitral insufficiency, in which the closure of the aortic valve may occur earlier in time; (5) vascular obstructions or increases in arterial pressure which cause prolongation of ventricular emptying times, e.g., as in pulmonary stenosis; (6) decrease in arterial pressure which decreases resistance to ventricular emptying and more rapid emptying and in turn more rapid closure of the aortic valve.

In right bundle branch block with delayed activation of the right ventricle, and in turn late closure of the pulmonic valve, there is abnormal splitting. This splitting varies with normal respiration. It is widened on inspiration and narrowed on expiration, but in contrast to the normal, the splitting is frequently wide even on expiration. In atrial septal defect there is volume overloading of the right ventricle, delayed emptying time for the right ventricle, delayed closure of the pulmonic valve, and resultant wide splitting of the pulmonic second sound. Here, however, there is little variation with respiration since phasic differences in volume load on the two ventricles tend to be neutralized by flow across the defect. Another factor may be that the already overloaded right ventricle in atrial septal defect may have difficulty in greatly increasing its filling coincident with the increased venous return during inspiration. These points have practical diagnostic significance.

The Valsalva maneuver, by increasing intrathoracic pressure, inhibits flow into the right ventricle. Right ventricular emptying time is shortened, the pulmonic valve closes earlier, and the pulmonic component of the second heart sound moves toward the aortic component so that they may become superimposed or may even cross over. Frequently, even in right bundle branch block, the wide splitting may be abolished by this maneuver and a single sound produced. In atrial septal defect, however, because of filling across the defect, the Valsalva maneuver usually fails to cause much variation in the splitting.

In left bundle branch block the situation is different. Here, because of late activation of the left ventricle, the aortic valve closes later and the aortic component of the second heart sound may actually follow the pulmonic component. There is still phasic variation in the splitting with respiration, but in this disturbance the splitting tends to narrow on inspiration and widen on expiration. ("paradoxical splitting.")

Thus, various aspects of splitting of the second heart sound may be of considerable diagnostic significance at the bedside. Splitting of the first heart sound is frequently detected, but thus far it has proved to be of little clinical significance. Right bundle branch block is a frequent cause of splitting of the first sound.

The intensity of the pulmonic second sound is important clinically, for example, in the diagnosis of pulmonary hypertension. It is not sufficient to know that P_2 is greater than A_2. The two components of the second sound at the pulmonic area (closure of the aortic and pulmonic valves) must be identified and ...nder component determined. T... ...ent that "there was evidenc...

the chest wall the more tense the area of the underlying skin or dermal diaphragm becomes. When the skin is stretched tight by firm pressure the transmission of high pitched sounds is favored low pitched ones are filtered-out. With quite firm pressure the transmission characteristics of the bell approach those of the regular stethoscope diaphragm By varying or lessening the pressure which is applied the frequency level of the transmitted sounds tends to be varied These features are particularly useful in detecting soft low pitched diastolic murmurs, such as the Carey Coombs murmur

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rhythms are well known and in general apply to those which originate in the left side of the heart. Recent studies have indicated however that similar gallop sounds which originate from the right side of the heart are not infrequent in conditions which place an extra load on this side of the circulation. These are generally loudest near the sternum near the xiphoid or in the epigastrium. Gallops in the right side of the heart are readily modified by respiration. As opposed to gallop rhythms from the left ventricle those from the right tend to be accentuated during the increased inflow produced by inspiration and tend to be diminished during the relatively decreased inflow produced by expiration or the Valsalva maneuver.

The normal third heart sound is thought to be due to vibrations produced in the left (or right) ventricle by rapid inflow of blood early in diastole or to momentary reclosure of the mitral (or tricuspid) valve or to both mechanisms. A third heart sound is commonly audible in children and young adults but it is rarely detected in normal persons after the age of 40. In this latter group the presence of a clear third heart sound should lead one to suspect cardiac failure as it then may carry the significance of a characteristic ventricular gallop even though the fast rate and typical gallop cadence are absent.

Frequently with fast rates, it is difficult to determine whether or not a gallop rhythm is of the atrial or ventricular variety. In such cases one is frequently helped by slowing the rate through careful carotid sinus massage. If the gallop stays with the second sound it is the ventricular type whereas if it moves with the first heart sound it is the atrial variety.

The foregoing comments raise the problem of simple timing of the heart sounds. Obviously the first and second sounds can usually be easily identified by their temporal relationships in the cardiac cycle i.e., there is a shorter time interval between the first and second sounds than between the second and first sounds. With faster rates however this may not be reliable. The characteristics of the sounds may be helpful i.e., the first sound is of lower pitch and longer duration and the sound is of higher pitch and shorter

tion. In difficult c obtained from the k sound is usually loude that the second soun base. This is not alw since in systemic hypert n the aortic second sound m sound heard at the apex stenosis the first soun loud at the base. Awareness other exceptions however one to avoid errors. Further problems of timing the apex the carotid pulse should be guideposts. The carotid pulse is the most reliable timing event a to the examiner. Criticisms that the in this pulse after ventricular contract may cause difficulty in timing have n been found to be clinically significant.

When multiple sounds are present, at the apex for example difficulty may arise in adequate timing. A useful procedure here is to identify the second sound at the base then keeping this sound in mind move the stethoscope rhythmically with the heartbeat down to the apex, carrying the identified second sound in the process. This maneuver has been termed "inching."[?] Occasionally in problems of timing one may wish to employ two stethoscope chest pieces each with tubing connections leading to a separate ear. The two chest pieces are then placed over separate areas of interest on the chest, and timing guideposts are detected and correlated. How this procedure might be fashioned should be obvious when tried.

Occasionally diastolic gallops are confused with the triple rhythm produced by systolic clicks. Appropriate timing and correlation of other data may eliminate this error. Systolic clicks (systolic gallops) are extra high-pitched sounds that may be divided into the early and the late varieties.[19] The middle or late systolic clicks heard loudest at the apex are usually of no pathologic significance. Their etiology is unknown but they may be due to traction on the pericardium. Clicks heard early in systole (ejection sounds) are usually of pathologic significance. They apparently are due to vibrations set up in the aorta or pulmonary artery thus may be divided into the a

the pulmonic types. Clicks may be single or multiple. The aortic clicks are usually heard best over the apex but may be quite loud at the base. They occur in aortic aneurysm, diffuse aortic dilatation, systemic hypertension, aortic stenosis, aortic insufficiency, coarctation of the aorta, and tetralogy of Fallot. The pulmonic clicks are heard best over the pulmonic area and are faint if heard at the apex. They occur in dilatation of the pulmonary artery, pulmonary hypertension, atrial septal defect, ventricular septal defect, pulmonary stenosis, thyrotoxicosis, A-V aneurysm, beriberi, Paget's disease, pregnancy, and anemia. Pulmonic clicks vary in intensity with respiration more than the aortic variety and tend to be accentuated during expiration and decentuated during inspiration.

Extracardiac sounds that are synchronous with the heartbeat ("xiphosternal crunch") may lead to errors in interpretation. Many are probably produced by compression of adjacent air-filled portions of the lung. These are readily ...ntified by their intimate relationship ... respiration since they are increased ... inspiration (and a deeply held in...ration) and decreased or abolished with deep expiration.

The misdiagnosis of mitral stenosis still tends to be a common pitfall. This seems to be frequently so in patients with left ventricular dilatation, especially that due to myocarditis. A mitral diastolic murmur common in these patients tends to be more of a "roar" than a "rumble," a characteristic which is helpful in auscultatory diagnosis. A protodiastolic gallop sound should not be misinterpreted as an opening snap. The ventricular gallop tends to be lower pitched, longer in duration, and occurs later in diastole. It should be remembered that since left ventricular gallops are dependent in part upon rapid inflow across the mitral valve, they are very unusual in mitral stenosis in which such rapid inflow is inhibited. Mitral stenosis may be misdiagnosed in still other situations, e.g., confusing diastolic murmurs may be produced in ventricular septal defects and patent ductus arteriosus with high flow across the mitral valve and in atrial septal defect with high flow across the tricuspid valve. Obviously, if all the clinical and laboratory data available are taken into consideration, such pitfalls will be avoided.

Occasionally, the normal first heart sound has a definite "presystolic" crescendo quality. Here the problem of mild mitral stenosis is frequently raised. In such cases, a simple clinical maneuver is frequently of value. If the patient holds his breath in inspiration, normally the presystolic crescendo components usually disappear and the first heard sound is "cleared-up." In mitral stenosis, however, the characteristic murmur usually remains.

Occasionally one is pressed to determine whether or not an extra sound which is heard at the apex closely following the "second sound" is due to an opening snap or to a loud split pulmonic second sound component transmitted to the apex. Auscultation at the base may not always solve the problem, since opening snaps may be quite loud there. The situation may frequently be resolved by careful auscultation in an area between the apex and the pulmonic area. One may then find a spot at which all three sounds are heard, i.e., the aortic valve closure sound, the pulmonic valve closure sound, and the opening snap. This is best detected during inspiration. To clarify the problem occasionally one may wish to utilize the afore-mentioned double stethoscope technique. Furthermore, the opening snap is often loudest during expiration, whereas the pulmonic second sound tends to be lost because of fusion with the aortic sound during this phase of respiration. Remember the presence of a "booming" first sound and an opening snap in mitral stenosis are good indications that the mitral valve is not rigidly calcified and fixed. This implies a potential for good operative results. Moreover, postoperative lengthening of the time interval between the second sound and the opening snap (2-O-S interval) may be indicative of a successful surgical result. This is so since left atrial pressure has been reduced and the time required for left ventricular pressure to drop below left atrial pressure (and thus opening of the A-V valve) has been prolonged.

A murmur which frequently causes much

debate is the apical systolic crescendo murmur. The mechanism of this peculiar murmur is unclear. It is usually a benign finding or at most indicative of minimal mitral insufficiency. From phonocardiography, it has been suggested that the benign may be differed from the pathologic murmur by the fact that the latter carries through the second sound, whereas the former stops before it, and that the latter has definite components in early systole and the former does not.

Another point of importance is the differentiation of "to and fro" murmurs *from continuous* murmurs. Occasionally, the murmur of a patent ductus is erroneously described as a "to and fro" systolic and diastolic murmur. The problem is obvious. The "to and fro" murmur is characteristic of aortic stenosis and insufficiency and indicates that the blood must change its direction of flow (and therefore the pause) for its production. The continuous murmur, however, is due to a continuous flow of blood from a high-pressure to a low-pressure area during systole and diastole (e.g., from aorta to pulmonary artery).

It should be remembered that all continuous murmurs are not due to patent ductus arteriosus. They may be due to venous hums, "mammary souffles" of pregnancy and lactation, aorta-pulmonary windows, sinus of Valsalva aneurysms and ruptures, pulmonary arteriovenous fistulae, coronary vessel A-V fistulae, hepatic angiomas, and any other A-V fistulae (e.g., in the chest or abdominal wall), ventricular septal defect with unsupported or deformed aortic cusp, coarctation of the aorta, pulmonary artery atresia with collateral circulation, coarctation of the pulmonary artery, variants of aortic insufficiency, thyrotoxicosis, total anomalous venous drainage, truncus arteriosus, and pseudotruncus. The uninitiated has even been misled by the hum from nasal oxygen therapy. Probably the most frequent error has been with respect to venous hums. These are usually loudest at the base of the neck, especially on the right side, and are frequently present in severe anemia. As opposed to patent ductus, they may be abolished by manual occlusion of the jugular v- the Valsalva maneuver, by placing the patient in the exaggerated Trendelenburg position (with auscultation during and immediately after assumption of this position), or by a combination of these. Mammary souffles can usually be abolished by firm pressure with the stethoscope head.

Pericardial friction rubs are occasionally misdiagnosed as "to and fro murmurs." This error may be avoided by recognizing the characteristics of rubs, which have a scratchy, shuffling quality with higher frequency components than most heart murmurs. The friction rub sounds superficial and closer to the ear and is accentuated by firm pressure with the stethoscope chest piece. Furthermore, friction rubs frequently have three distinct components, the first related to atrial systole (presystole), the second to ventricular systole, and the third to early-middle ventricular diastole. With auricular fibrillation, only two components can be heard (ventricular systole and diastole) or occasionally only one component (ventricular systole). It has been noted that with a normal sinus rhythm, the persistence of a systolic component alone generally eliminates the possibility of a pericardial friction rub as the cause of a scratchy sound.[2] The subsequent course of the patient and the correlation of all available clinical data generally settles any problems.

An erroneous diagnosis of pericarditis is occasionally made in thyrotoxicosis (or other high-output states) because of the presence of a scratchy systolic noise heard along the left sternal border. This is probably due to high flow in the pulmonary artery, and it can usually be differentiated from a pericardial rub by the absence of well-developed presystolic or early mid-diastolic components.

Some comment should probably be made regarding the so-called "functional" murmurs. They are most frequently systolic in time, loudest at the pulmonic or occasionally the mitral area, faint to moderate in intensity, and of a blowing quality. They tend to be temporally inconstant and tend to vary with respiration and body position. Occasionally, functional murmurs in diastole may be noted, especially during pregnancy, in severe anemia (especially sickle cell or other chronic anemias),

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in thyrotoxicosis. At times a soft pulmonary diastolic murmur may be detected in persons who are otherwise normal. Most frequently these persons have been young women with thin chests. The cause of these murmurs is unclear but perhaps some truly represent mild pulmonic insufficiency. The functional murmurs from so-called relative stenosis or insufficiency of the various valves are well known.

Several auscultatory tricks have not been presented. One of these is the use of amyl nitrite in the distinction of mitral insufficiency from aortic stenosis and the differential diagnosis of isolated pulmonary stenosis, tetralogy of Fallot, and ventricular septal defect.[11] Another is the use of vasopressors in the differentiation of the pansystolic murmurs of mitral insufficiency, tricuspid insufficiency, and ventricular septal defect.[12] Most other helpful clues in cardiac auscultation are obvious and regularly used by the well trained clinician. The points which were selected for discussion are those which are not only helpful clinically but which also are occasion[illegible] confusing or lead to misinterpretation. [illegible]uld be emphasized however that [illegible]typical findings are not always identi[illegible] [illegible] and clear-cut clinically in any given [illegible], and that one should strive to integrate all available data derived by whatever feasible means before final decisions are made.

REFERENCES

1. Rappaport, M.B., and Sprague, H. B. Effects of tubing bore on stethoscope efficiency. AM. HEART J. 42:602, 1951.
2. Levine, S. A., and Harvey, W. P. Clinical auscultation of the heart, Philadelphia, 1959, W. B. Saunders Company.
3. Leatham, A. Splitting of first and second heart sounds, Lancet 2:607, 1954.
4. Leatham, A. Auscultation of the heart, Lancet 2:703 and 757, 1958.
5. McKusick, V. A., Reagan, W. P., Santos, G. W., and Webb, G. N. Splitting of heart sounds, spectral phonocardiographic evaluation of clinical significance, Am. J. Med. 19:849, 1955.
6. Schilder, D. P., and Harvey, W. P. Confusion of tricuspid incompetence with mitral insufficiency—a pitfall in the selection of patients for mitral surgery. AM. HEART J. 54:352, 1957.
7. McKusick, V. Cardiovascular sound in health and disease, Baltimore, 1958, Williams & Wilkins Company.
8. Butterworth, J. S., Chassin, M. R., McGrath, R., and Reppert, E. H. Cardiac auscultation, New York, 1960, Grune & Stratton, Inc.
9. Ongley, P. A., Sprague, H. B., Rappaport, M. B., and Nadas, A. S. Heart sounds and murmurs. A clinical and phonocardiographic study, New York, 1960, Grune & Stratton, Inc.
10. Minhas, K., and Gasul, B. M. Systolic clicks: clinical, phonocardiographic, and hemodynamic evaluation, AM. HEART J. 57:49, 1959.
11. Vogelpoel, L., Nellen, M., Swanepoel, A., and Schrire, V. Use of amyl nitrite in diagnosis of systolic murmurs, Lancet 2:810, 1959.
12. Soloff, L. A., Cortes, F., Winters, W. L., Jr., and Zatuchni, J. Pansystolic regurgitant murmur: simple method of identifying its anatomic source, Am. J. M. Sc. 237:744, 1959.

Clinical communications

Partial persistent atrioventricular canal simulating pure mitral regurgitation

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The two principal anatomic malformations which comprise the partial or incomplete form of persistent atrioventricular (A V) canal are an interatrial septal defect of the ostium primum variety and a cleft in the anterior leaflet of the mitral valve. The atrial septal defect is usually large, and the predominant functional abnormality is the left-to-right shunt at the atrial level In addition the cleft mitral leaflet generally produces valvular regurgitation of minimal to moderate severity In such patients the interatrial defect serves to decompress the left atrium and prevents elevation of left atrial pressure and marked enlargement of this chamber We have had the opportunity however to study two patients with partial persistent A V canal who were initially considered to have mitral regurgitation of rheumatic origin and who only after detailed study were shown to have small interatrial communications. A description of the clinical hemodynamic and pathologic findings in the patients with this unusual variant of A V canal forms the subject of this report.

Clinical summaries

Case 1 (02 74-33). T A. was a 13-year-old schoolboy whose growth and development had been slow throughout his life. He was not examined by a physician until he was 6 years old, at which time he was hospitalized for 4 months because of fever and tachypnea, and was found to have apical systolic and diastolic murmurs and an enlarged heart. He was considered to have acute rheumatic fever After this illness he was unable to play actively without excessive fatigue, but he attended school. Between the ages of 11 and 13 years the patient was hospitalized on four additional occasions, once because of fever and abdominal pain and other times because of left-sided and right sided heart failure. Determinations of C-reactive protein and antistreptolysin titers were always normal. Cardiac examinations always revealed the systolic and diastolic murmurs. Electrocardiograms taken when he was in sinus rhythm showed P-R prolongation when corrected for heart rate, but after he was 12 years old, atrial fibrillation was present. In November 1959 he was admitted to the National Heart Institute because of persistent dyspnea and orthopnea.

Physical examination showed that the patient was a small, poorly developed, and cachectic child who weighed only 24 kilograms and appeared to be chronically ill. The blood pressure was 110/87 mm. Hg, and the pulse was grossly irregular The neck veins were dilated and showed large systolic pulsations There was a prominent precordial bulge, a striking left ventricular lift, and a modest right ventricular lift. The second sound over the pulmonic area was palpable, and on auscultation was split, with a loud pulmonic component. The split remained fixed, even during the Valsalva maneuver A Grade 3/6 pansystolic murmur was best heard at the apex but was well transmitted over the entire precordium. At the lower left sternal border there appeared to

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Fig. 1. Chest roentgenograms in the posteroanterior (*top*) and lateral (*bottom*) projections in Patient T. A.

to a separate systolic murmur which increased with inspiration. An early diastolic sound, which was followed by a Grade 3/6 mid-diastolic rumbling murmur was also heard at the apex. The liver was enlarged to below the level of the umbilicus; there was no peripheral edema.

Cardiac fluoroscopy and radiography demonstrated massive enlargement of the heart, with particular prominence of both right and left atria (Fig. 1). The pulmonary vascularity was not increased. The electrocardiogram (Fig. 2) revealed atrial fibrillation, left axis deviation, digitalis effect, and left ventricular hypertrophy. On the basis of the foregoing findings, observers considered the patient to have rheumatic mitral regurgitation.

At cardiac catheterization the right ventricular pressure was elevated to 55/15 mm. Hg, and the *pulmonary artery could not be entered. The tip of the catheter repeatedly refluxed from the right ventricle into the right atrium, which indicated the presence of tricuspid regurgitation. The mean pressure in the right atrium was 13 mm. Hg and the v waves peaked at 17 mm. Hg.* Surprisingly the catheter passed into the left atrium through an interatrial communication. The peaks of the v waves in this chamber were 27 mm. Hg, and the mean pressure was 15 mm. Hg. A Kr^{85}-inhalation test[4] demonstrated that a small left-to-right shunt entered the right atrium, and the calculated pulmonary-systemic flow ratio was 1.4/1.0. A selective left ventricular angiocardiogram demonstrated massive mitral regurgitation and, also, opacification of the right atrium from the left.

With the additional information provided by the hemodynamic studies it appeared likely that the patient had congenital heart disease—an ostium primum defect with cleft mitral and tricuspid valves. At operation there was massive enlargement of both atria and a systolic thrill in each. After the institution of cardiopulmonary bypass a left atriotomy was made (Fig. 3). There was a complete cleft in the anterior leaflet of the mitral valve, and a small ostium primum interatrial defect which was less than 1 cm. in diameter. The thickened margins of the cleft were approximated with interrupted sutures, and the defect was closed similarly. The valve appeared to be competent after the repair. Inspection of the tricuspid valve after right atriotomy revealed that regurgitation of blood was occurring between the anterior and septal leaflets. No discrete cleft in either leaflet could be discerned, and the tricuspid annulus was plicated in this area. After operation the general condition of the patient was poor, and on the day after the procedure, cardiac arrest occurred and resuscitation was unsuccessful.

PATHOLOGIC FINDINGS. The heart weighed 350 grams, and the left atrium was greatly enlarged (Fig. 4). The surgically closed mitral cleft extended from the mid-portion of the free margin of the anterior leaflet to the annulus dividing the leaflet into anterior and posterior halves. The chordae tendineae from the anterior portion of the cleft leaflet, in addition to inserting normally into the anterolateral papillary muscle of the left ventricle, also inserted into the superior ridge of the muscular ventricular septum (Fig. 5). The accessory chordae tendineae to the ventricular septum were thickened, shortened, and adherent to one another. They did not appear to interfere with the outflow of blood from the left ventricle. The chordae tendineae from the posterior portion of the anterior mitral leaflet inserted normally into the posteromedial papillary muscle. The left ventricle was hypertrophied and dilated. Although no ventricular septal defect was present, the membranous portion of the septum was thickened and malformed. The ostia of both coronary arteries were located in the sinus of Valsalva behind the right anterior aortic cusp; the right coronary artery was markedly hypoplastic but the left was normal. Both the aortic ring and

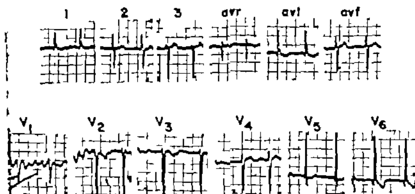


Fig. 2. Electrocardiogram of Patient T. A.

the ascending aorta were small. The right atrium was moderately dilated, and the foramen ovale was closed. The tricuspid chordae tendineae, although delicate, were extremely short and few in number. There was no cleft in any tricuspid leaflet, but a portion of the septal leaflet adjacent to the anterior leaflet was absent. This malformation probably accounted for the tricuspid regurgitation which had been present. The small interatrial communication was located immediately above the absent portion of the septal leaflet. The pulmonic valve in addition to three normal cusps contained a fourth rudimentary one.

Case 2 (00-94-43). N. R., a 31-year-old woman was known to have had heart disease since the age of 12 years, when she was thought to have had acute rheumatic fever. She was given digitalis in her late teens because of recurrent episodes of paroxysmal atrial tachycardia. Aside from mild exertional dyspnea, however, she felt well and completed a pregnancy at the age of 19 years without difficulty. When she was 27 years old, she developed atrial fibrillation and experienced exertional dyspnea and fatigability. Over the next 4 years these symptoms progressed and she developed signs of congestive heart failure.

On admission to the National Heart Institute she was found to be thin and anxious and appeared to be dyspneic at rest. Her blood pressure was 110/60 mm. Hg and the peripheral pulse was grossly irregular. The jugular venous pulse exhibited prominent v waves. Both right and left ventricular lifts were present. In addition to an apical systolic thrill there was a Grade 4/6 pansystolic murmur loudest at the apex and transmitted well into the axilla. A prominent third heart sound was followed by a short low-pitched apical diastolic rumbling murmur. At the left sternal border there was a Grade 4/6 pansystolic murmur accompanied by a high-pitched mid-diastolic murmur which increased in intensity with inspiration. In the pulmonic area there was a short ejection murmur and the second sound was accentuated and maintained a fixed split throughout the respiratory cycle. The liver was enlarged to 5 cm. below the right costal margin and expanded with cardiac systole. Mild pitting edema of the ankles was present.

The sedimentation rate was n[illegible] and the C reactive protein was negative. Roentgenologic examinations demonstrated moderate cardiac enlargement with prominence of the left atrium and left ventricle (Fig. 6). The pulmonary vascularity appeared to be normal and no valvular calcifications were seen. The electrocardiogram revealed atrial fibrillation, left ventricular hypertrophy, and digitalis effect (Fig. 7). The patient was considered to have rheumatic heart disease with mitral and tricuspid regurgitation. At cardiac catheterization the pulmonary arterial (22/8 mm. Hg) and right ventricular (24/5 mm. Hg) pressures were normal. The catheter unexpectedly crossed from the right atrium to the left, and the mean pressure in each chamber was 4 mm. Hg. A Kr^{85}-inhalation test confirmed the presence of a left-to-right shunt which entered the right atrium, and the calculated pulmonary-systemic flow ratio was 1.7/1. Indicator-dilution curves demonstrated that the shunt originated from the left ventricle. In order to exclude the possibility of an associated ventricular septal defect, a selective angiocardiogram with left ventricular injection was



Fig. 3. The completely cleft anterior mitral valve leaflet and small interatrial communication encountered after cardiotomy.

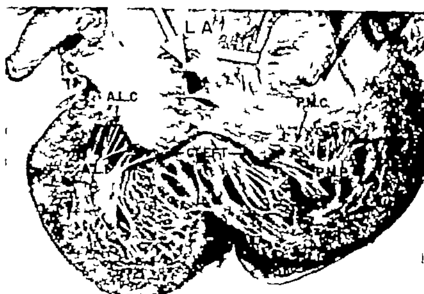


Fig 4 Autopsy appearance of the heart of Patient T A. The left atrium (*L A*), mitral valve, and left ventricle (*L V*) are shown. The left atrium is markedly dilated, and the left ventricle is hypertrophied and dilated. The sutures which close the small ostium primum defect (*white arrow*) have been removed. The defect is located at the apex of the cleft in the anterior mitral leaflet. The chordae tendineae which extend to the anterolateral (*A L P*) and posteromedial (*P M P*) papillary muscles are normal. The anterolateral (*A L C*) and posteromedial (*P M C*.) commissures are designated for orientation purposes.

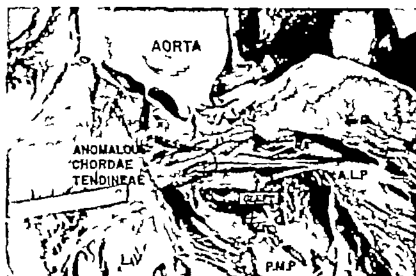


Fig 5 The left ventricle (*L V*), aortic valve and aorta of Patient T A. Anomalous chordae tendineae (*demarcated by the broken line*) are seen to extend from the anterior portion of the cleft anterior mitral leaflet to the crest of the ventricular septum immediately beneath the aortic valve cusps. The anterolateral (*A L P*) and posteromedial (*P M P*) papillary muscles are labeled.

carried out.[8] This demonstrated severe mitral regurgitation into an enlarged left atrium, opacification of the right atrium through an interatrial septal defect, and an intact ventricular septum (Fig 8) These findings were considered to support the diagnosis of ostium primum defect with a cleft mitral valve, although the possibility of an ostium secundum defect with rheumatic mitral regurgita-



Fig. 6. Preoperative chest roentgenogram in the posteroanterior projection in Patient N. R.

tion could not be excluded. At operation a right atriotomy was made and a small crescent-shaped defect, which measured 1 by 2 cm. in diameter was found in the lowermost portion of the interatrial septum. When the superior margin of the defect was retracted upward, a complete cleft in the anterior leaflet of the mitral valve was revealed. This was repaired with continuous sutures in two layers. The interatrial defect was then closed with a prosthetic patch. The patient tolerated the operation well and made a satisfactory recovery.

After discharge the patient felt that she was improved and was able to return to part-time employment in a sedentary job. After 3 months, however she began to develop increasingly severe exertional dyspnea and was again troubled with retention of fluid. Signs of congestive heart failure progressed over the next several months and she was rehospitalized in July 1959. The systolic murmur in the tricuspid area now had a loud, cooing quality and became strikingly accentuated with inspiration. The pulmonic second sound moved normally with respiration. The other auscultatory findings were similar to those of her preoperative examination. The liver which had become further enlarged to 12 cm. below the right costal margin, was firm and pulsatile and a small amount of ascitic fluid was present. The chest roentgenogram revealed a considerable increase in the size of the left atrium (Fig. 9). The electrocardiogram again showed atrial fibrillation, left ventricular hypertrophy and digitalis effect.

The patient underwent right heart and transbronchial left heart catheterization. The pulmonary arterial pressure was now elevated to 54/20 mm. Hg and the right atrial pressure tracing exhibited the contour characteristic of tricuspid regurgitation. The right atrial mean pressure was 12 mm. Hg. There was no evidence of a residual shunt. The left atrial mean pressure was 27 mm. Hg and the waves were 55 mm. Hg (Fig. 10). There was a mean diastolic gradient of 10 mm. Hg across the mitral valve.

Because of the deterioration in the condition of the patient, and the evidence of significant mitral and tricuspid regurgitation, it was thought that a second attempt at surgical correction was indicated. At operation there was an intense systolic thrill within the left atrium, which was large and tense. Inspection through a left atriotomy revealed that the cleft in the anterior leaflet had been incompletely repaired. The residual valvular cleft, which was about 2.5 cm. in length was closed with interrupted mattress sutures. After completion of the repair the valve appeared to be competent but somewhat stenotic. The anterolateral commissure, which was apparently fused was incised to yield an orifice which would accept two fingers with ease.

The patient's convalescence was complicated by a massive hemorrhage from the upper gastrointestinal tract on the sixth postoperative day. After a partial gastrectomy for a bleeding prepyloric ulcer she recovered satisfactorily. She continued to have evidence of mitral regurgitation, however and remained severely limited after her discharge. Eight months later she died in chronic congestive heart failure.

PATHOLOGIC FINDINGS. At necropsy the heart was found to be enlarged; it weighed 470 grams. All chambers were dilated and hypertrophied. The

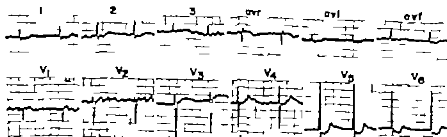


Fig. 7. The electrocar Patient N. R.



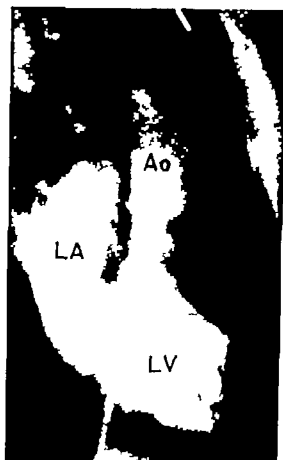


Fig. 4. Selective left ventricular angiocardiogram of Patient N. R. which demonstrates gross mitral regurgitation. Lateral views exposed during ventricular diastole (*left*) and ventricular systole (*right*) are shown. During systole the left atrium (*LA*) increases strikingly in size whereas the left ventricle (*LV*) diminishes in size. *Ao*, Aorta.

right ventricle measured 7 mm. in thickness, and the left 12 mm. The prosthetic patch covered by opaque endocardium, occupied and completely closed a crescent-shaped defect in the lowermost portion of the interatrial septum. Although the tricuspid valve was not cleft and its chordae tendineae were normal, a portion of the septal leaflet was absent and in Patient T. N. it was believed that this abnormality had been responsible for the tricuspid regurgitation. The pulmonic valve and pulmonary trunk were mildly dilated. There was a jet lesion on the posterior wall of the left atrium. The mitral valve ring measured only 7 cm. in circumference compared to 12 cm. for the tricuspid valve ring. There was no evidence of a remaining cleft in the anterior leaflet of the mitral valve and the silk sutures in its mid-portion were covered by endocardium. Although both mitral leaflets were thickened, their appearance did not resemble rheumatic valvulitis. Anomalous chordae tendineae which were thickened and fused, extended from the ventricular aspect of the most distal margin of the anterior mitral leaflet to the superior crest of the muscular ventricular septum. These accessory chordae did not apparently cause any obstruction to outflow of blood from the left ventricle. The chordae tendineae which inserted into the left ventricular papillary muscles were normal.

Comment

Prior to cardiac catheterization both of the patients described were considered by most observers to have rheumatic heart disease with predominant mitral regurgitation. Both patients had had febrile illnesses in childhood which were thought to have been acute rheumatic fever. On physical examination each had *left ventricular prominence and a loud* pansystolic apical murmur, an early diastolic sound ushered in the mid-diastolic rumbling murmur which is so characteristic of massive mitral regurgitation. The electrocardiograms showed atrial fibrillation and were compatible with left ventricular hypertrophy. Neither patient had an RSR

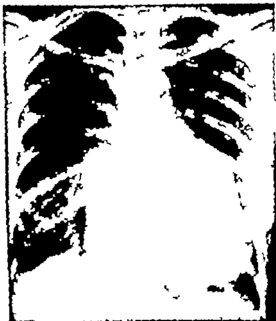


Fig 9 Chest roentgenogram of Patient N R taken 6 months after closure of the atrial septal defect and incomplete repair of the mitral valve. The posteroanterior projection demonstrates striking enlargement of the left atrium and ventricle in comparison to preoperative films (see Fig 6).

pattern in leads from the right precordium Patient N R had a normal electrical axis, and although Patient T A exhibited left axis deviation of the terminal electrical forces this deviation was less than that usually encountered in patients with A V canal The roentgenograms revealed gross left atrial and left ventricular enlargement without evidence of increased pulmonary vascularity

Cardiac catheterization in each patient revealed a left-to-right shunt into the right atrium and an interatrial communication which was crossed by the catheter The unusually small size of the defects was predicted from the finding of a small shunt in the presence of striking left atrial enlargement. In Patient T A there was, in addition a pressure gradient between the atria

Retrospectively the presence of fixed splitting of the second heart sound in the pulmonary area in both patients should have suggested the presence of an inter atrial septal defect prolongation of the P R interval repeatedly seen in Patient T A has frequently been observed in patients with A V canal[4] but in this instance was mistakenly attributed to active rheumatic fever

Burchell and co-workers[3] in a recent comprehensive review of the electrocardiographic findings in patients with endocardial cushion defects, concluded that the presence of the typical vector loop in a young individual with a large left-to-right interatrial shunt was almost pathognomonic of a defect of the ostium primum type Although all of the patients with the complete form of persistent A V canal studied by these authors had the characteristic electrocardiographic pattern superior orientation and counterclockwise rotation of forces in the frontal plane occasionally a patient with the partial form failed to show this configuration It would seem correct to conclude therefore on the basis of their report and the two patients described herein that the absence of the typical electrocardiographic features does not necessarily exclude the presence of an ostium primum type of atrial septal defect

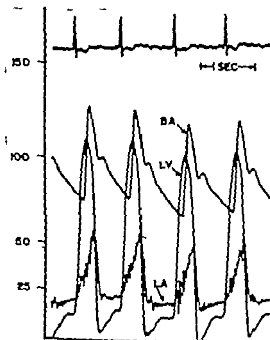


Fig 10 Simultaneous left atrial (LA), left ventricular (LV), and brachial arterial (BA) pressure pulses obtained 6 months after the initial operation in Patient N R. The left atrial pressure was obtained by transbronchial puncture and the left ventricular pressure by percutaneous puncture of this chamber

The primary surgical problem in the type of malformation presented by the patients described is the correction of the mitral regurgitation. In Patient N.R. the mitral cleft was not completely repaired by the first operation and closure of the interatrial defect eliminated the vent through which the left atrium was being decompressed. After this procedure her condition deteriorated rapidly. Within 6 months the mean left atrial pressure had risen from 4 to 27 mm. Hg, the left atrium had become massively enlarged, and severe pulmonary hypertension had developed. Although at the time of the second operation the cleft was completely repaired, she continued to have evidence of considerable mitral regurgitation. In Patient T. A. the cleft in the anterior mitral leaflet was also completely closed, but the loud murmur of mitral regurgitation persisted during the postoperative period. Residual regurgitation probably contributed to his death. Other authors have also stressed ... hazard of closing an atrial septal defect ... it correcting associated mitral re... ...ion in patients with the usual form ...rtial persistent A V canal.[4,5]

As demonstrated by Edwards,[6] the persistence of mitral regurgitation after surgical repair in these two patients may have been related to the presence of the accessory chordae tendineae which extended from the margins of the cleft to the ventricular septum (Fig. 5). These anomalous chordae, which have no counterpart in the normal heart, are a constant feature of endocardial cushion defects and appear to be pathognomonic of these malformations.[7] Although prior to operation these chordae provide support for the margins of the cleft during ventricular systole, they serve no useful function after the cleft has been repaired. Indeed, by restraining the apposition of the anterior against the posterior leaflet they may actually produce incompetence of the valve. Edwards has suggested, therefore, that all of the chordae which insert into the margins of the cleft be divided. Failure to appreciate the significance of these structures in the two patients reported on herein probably accounted for the persistent mitral regurgitation which each demonstrated.

Both patients also had tricuspid regurgitation but no cleft of the tricuspid valve could be recognized either at operation or at postmortem examination. A portion of the septal leaflet in each case, however, was absent. This malformation does not lend itself so readily to surgical correction as does a discrete cleft; plication of the septal portion of the annulus in Patient T.A. was of questionable value.

Summary

Patients with persistent partial atrioventricular canal and only small interatrial communications may present the clinical features of pure mitral regurgitation. Two such individuals who on clinical examination were mistakenly considered to have rheumatic mitral regurgitation are described. The roentgenographic findings supported this diagnosis, and the electrocardiograms did not exhibit the vector loop characteristic of an endocardial cushion defect. Cardiac catheterization made possible the correct diagnosis, however, and at operation each patient was found to have a cleft anterior mitral leaflet and an unusually small interatrial defect of the ostium primum type. Problems which relate to the diagnosis and surgical management of this unusual variant of persistent A V canal are discussed.

REFERENCES

1. Sanders, R. J., and Morrow, A. G.: The identification and quantification of left-to-right circulatory shunts: a new diagnostic method utilizing the inhalation of a radioactive gas, Kr[85], Am. J. Med. 26:508, 1959.
2. Braunwald, E., Morrow, A. G., and Cooper, T.: Left ventricular angiocardiography in the diagnosis of persistent atrioventricular canal and related anomalies, Am. J. Cardiol. 4:802, 1959.
3. Burchell, H. B., DuShane, J. W., and Brandenburg, R. O.: The electrocardiogram of patients with atrioventricular cushion defects (defects of the atrioventricular canal), Am. J. Cardiol. 6:575, 1960.
4. Watkins, E., Jr., and Gross, R. E.: Experiences with surgical repair of atrial septal defects, J. Thoracic Surg. 30:469, 1955.
5. Gerbode, F., Johnston, J. B., Robinson, S., Harkins, G. A., and Osborn, J. J.: Endocardial cushion defects: diagnosis and technique of surgical repair, Surgery 49:69, 1961.
6. Edwards, J. E.: The problem of mitral insufficiency caused by accessory chordae tendineae in persistent common atrioventricular canal, Proc. Staff Meet. Mayo Clin. 35:299, 1960.

7. Braunwald, E., Ross, R. S., Morrow, A. G., and Roberts, W. C.: Differential diagnosis of mitral regurgitation in childhood: clinical pathological conference at the National Institutes of Health, Ann. Int. Med. 54:1223, 1961.
8. Wakai, C. S., and Edwards, J. E.: Pathologic study of persistent common atrioventricular canal, Am. Heart J. 56:779, 1958.
9. Wakai, C. S., and Edwards, J. E.: Developmental and pathologic considerations in persistent common atrioventricular canal, Proc. Staff Meet. Mayo Clin. 31:487, 1956.
10. Rogers, H. M., and Edwards, J. E.: Incomplete division of the atrioventricular canal with patent interatrial foramen primum (persistent common atrioventricular ostium), Am. Heart J. 36:28, 1948.
11. Campbell, M., and Missen, G. A. K.: Endocardial cushion defects: common atrioventricular canal and ostium primum, Brit. Heart J. 19:403, 1957.
12. Paul, M. H.: Endocardial cushion defects: persistent common atrioventricular canal and persistent ostium primum, Pediat. Clin. North America 1011, 1958.
13. Kiely, B., Adams, P., Jr., Anderson, R. C., and Lester, R. G.: The ostium primum syndrome, A.M.A. J. Dis. Child. 96:381, 1958.
14. Toscano-Barboza, E., Brandenburg, R. O., and Burchell, H. B.: Electrocardiographic studies of cases with intracardiac malformations of the atrioventricular canal, Proc. Staff Meet. Mayo Clin. 31:513, 1956.
15. Beregovich, J., Bleifer, S., Donoso, E., and Grishman, A.: The vectorcardiogram and electrocardiogram in persistent common atrioventricular canal, Circulation 21:63, 1960.
16. Ellis, F. H., Jr., McGoon, D. C., and Kirklin, J. W.: Surgical management of persistent common atrioventricular canal, Am. J. Cardiol. 6:598, 1960.
17. Cooley, D. A.: Results of surgical treatment of atrial septal defects, Am. J. Cardiol. 6:605, 1960.
18. McGoon, D. C., DuShane, J. W., and Kirklin, J. W.: The surgical treatment of endocardial cushion defects, Surgery 46:185, 1959.

Rheumatic fever in the tropics

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Several investigators have postulated that geography and climate are important governing factors in the pathogenesis, incidence, and morbidity of rheumatic fever.[1,3] Some have claimed that the disease is infrequently encountered or ab- in some tropical areas.[1,4] In an attempt dy these concepts that to others[4,4] acceptable we have been prompted port on our experience with this disease in San Juan, Puerto Rico.

San Juan is located on the northeast coast of Puerto Rico at latitude 18° 28' north and longitude 66°7' west. It is surrounded by the waters of the Atlantic Ocean and San Juan Bay. The climate is tropical. The difference between the average temperatures of the warmest and the coolest months is only about 5.6°F. The average annual rainfall is 60.00 inches with a fairly even distribution throughout the year.[7]

That rheumatic fever is present in Puerto Rico was first confirmed in 1930 by Smetana[8] after he performed an autopsy on a 15-year-old Puerto Rican boy and encountered the typical pathologic findings of the disease. In spite of the evidence already collected, young continentals who suffered from active rheumatic fever were advised to come to Puerto Rico to recover in the belief that the geographic and climatic changes would be beneficial.[4] After a thorough analysis of the accepted textbooks of cardiology and publications in reputed journals[4,11] we are at a loss to explain why many authors persist in emphasizing *that rheumatic fever is rare in the tropics* in spite of the clinical material, autopsy figures, and additional data presented independently by investigators from our midst which reveal that rheumatic heart disease is the basic etiology for 17 to 32 per cent of all cardiac patients who are observed in Puerto Rico.[4,4]

Material and results

Our data are obtained from the study of 300 native born adult Puerto Ricans with rheumatic fever from the medical service of one of our charity hospitals. The patients whom we have seen during the last 8 years are presented in an attempt to evaluate the clinical picture, the natural history, and the morbidity of the disease as it occurs in Puerto Rico. It must be emphasized that our clinical material comes from an indigent population and that our results may not compare with other studies among patients under better

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Table I Distribution by age

Years	Acute rheumatic fever	Rheumatic heart disease	Total
12–19	71	60	131
20–29	23	50	73
30–39	4	42	46
40–49	3	26	29
50–59	0	15	15
60 or more	0	6	6
Total	101	199	300

economic conditions. A history of poor diet was always obtained. One hundred and one patients fulfilled the modified Jones criteria for acute rheumatic fever as recommended by the American Heart Association.[11] One hundred and ninety nine cases fulfilled the accepted criteria for a diagnosis of rheumatic heart disease according to the New York Heart Association.[12] All patients studied were 12 years of age or older when we first saw them. Table I illustrates the distribution of the illness according to age. It is noted that of the 101 patients who had acute rheumatic fever 94 were less than 30 years of age. The distribution of cases of rheumatic heart disease was about the same before and after the age of 30. Although classic acute rheumatic fever has its highest incidence among children and adolescents, it is of interest that in a few cases the condition was first noticed in the older decades of life.

The distribution of cases by sex and race is shown in Table II. The disease was most commonly encountered in females, especially so in the rheumatic heart disease group. White persons seem to be affected twice as often as colored, but when the proportion of white to colored population in Puerto Rico is taken into account, it appears that the disease occurs with about equal frequency in both races.

Table III illustrates the frequency of the most prominent symptoms. Of the 101 patients who had acute rheumatic fever 99 complained of arthritis which was of the polyarticular and migratory type; 2 had arthralgias. Of the 199 patients who had rheumatic heart disease 111 had a past history of [illegible]tis and an additional 23 had arthralgias. In 32.7 per cent of the patients with rheumatic heart disease there was no history of symptoms in the joints. Twelve patients with acute rheumatic fever and 11 with rheumatic heart disease had also had chorea. Skin lesions had occurred in 11 of the 300 patients. After arthritis, fever was the most common symptom and was present in 196 patients. It had been of variable duration and intensity. Sore throat had been a rather common complaint and because of its severity 23 patients had had tonsillectomies. Epistaxis was present in 36 patients. Chest pain, palpitations and cough were fairly common complaints, especially among the patients with rheumatic heart disease, in whom greater pathologic changes in the heart and lungs are expected. Cough which was productive of blood occurred in 44

Table II Distribution by sex and race

Sex and race	Acute rheumatic fever	Rheumatic heart disease	Total
Female	59	126	185
Male	42	73	115
Total			300
White	71	129	200
Colored	32	68	100
Total			300

Table III Frequency of symptoms

Symptom	Acute rheumatic fever (101 cases)	Rheumatic heart disease (199 cases)	Total (300 cases)
Arthritis	99	111	210
Arthralgias	2	23	25
Chorea	12	11	23
Skin lesions	8	3	11
Fever	89	107	196
Sore throat	67	71	138
Epistaxis	13	23	36
Tonsillectomy previously	5	18	23
Chest pain	9	97	106
Palpitations	11	75	86
Cough	7	87	94
Hemoptysis	1	44	45

Table IV Significant symptoms in 101 patients with acute rheumatic fever

Symptom		Number of patients
Polyarthritis		89
Heart murmurs		77
Chorea		12
Erythema marginatum		5
Beta hemolytic streptococcus (throat)	(78)	51
Hyperemic throat		63
Fever		83
Sinus tachycardia		50
Leukocytosis		55
Abnormal sedimentation rate	(100)	95
Abnormal C-reactive protein	(39)	29
Diastolic gallop		3
Abnormal electrocardiograms	(70)	22
Subcutaneous nodules		6

of the patients with cardiac symptoms, but only once in a patient with acute [illegible]eumatic fever Hemoptysis was explained [illegible] the basis of a rupture of the bronchial [illegible]es, congestive failure, and pulmonary [illegible]

The frequency of the various symptoms in the 101 patients with acute rheumatic fever is depicted in Table IV The most frequently encountered abnormal finding was an elevated sedimentation rate, which occurred in 95 ptients.

Next in frequency was polyarthritis, which occurred in 89 patients 10 other patients came to us when the manifestation of inflammed joints had disappeared Heart murmurs were next in frequency Sinus tachycardia was encountered in 50 per cent of the patients, and only 3 had a diastolic gallop There were only 12 cases of chorea and 5 of erythema marginatum. Sixty three patients were found to have a hyperemic throat, and throat cultures of 51 of 78 patients who were examined were positive for beta hemolytic streptococci Leukocytosis occurred in about one half of the patients. The C reactive protein was significantly elevated in 29 of the 39 patients who were tested The electrocardiogram was abnormal in 22 of the 70 patients in whom a recording was taken

We were able to study the seasonal incidence of the first episode of arthritis in 120 patients This is shown in Table V A relatively higher incidence was noted in the spring and winter and a lower incidence in the autumn.

The age at onset of the first episode of arthritis was determined in 205 patients and is shown in Table VI The greatest incidence occurred in the second decade of life. It is interesting to note that in 3 instances the first episode of arthritis occurred in the forties so that although rheumatic fever is considered to be a dis ease of early life it may occur in middle age

The distribution of the initial involvement of the joints was determined in 147 patients and is illustrated in Table VII The joints of the lower extremities especially the feet, the ankles and the knees were first affected in 122 patients. In the other 25 patients the joints initially involved were in the upper extremities. The arthritis was characteristically polyartic ular and migratory in character

In the 199 patients with rheumatic heart disease the diagnosis was established on the basis of specific physical findings, x ray films and electrocardiographic and phono-

Table V Seasonal incidence of polyarthritis in 120 patients

Season	Mean temperature*	Mean relative humidity*	Number of patients
Spring	77 0	77 3	37
Summer	80 1	77 5	26
Autumn	80 2	80 3	11
Winter	75 2	79 0	46

*See reference 7

Table VI Age at first episode of arthritis in 204 patients

Age (yr)	Number of patients
Less than 5	6
5-9	28
10-19	123
20-29	37
30-39	7
40 or more	3
Total	204

Table VII. Location of initial involvement of joints in 147 patients

Location	Number of patients
Feet and ankles	53
Knees	64
Hips	5
Fingers and wrists	10
Elbows	10
Shoulders	5
Total	147

Table VIII. Valve involved in 199 patients with rheumatic heart disease

Valve		Number of patients
Mitral		140
Insufficiency	29	
Stenosis	21	
Both	90	
Aortic		5
Mitral and aortic		47
Mitral and tricuspid		7
Total		199

cardiographic studies. Cardiac catheterization was performed in a small number of patients. In some cases autopsies were available. At the time of examination evidence of activity of the rheumatic process was present in 116 patients with cardiac disease. The presence of nodules, involvement of the joints, choreiform movements, erythema, low-grade fever, pericarditis, persistent tachycardia, elevated sedimentation rate and white blood cell counts, and changing electrocardiograms were considered to be evidence of activity provided that there was no other discoverable condition to cause it. The distribution of valvular involvement is presented in Table VIII. The mitral valve alone was involved in 140 patients, most had double lesions. Mitral insufficiency alone occurred in 29 patients and mitral stenosis in 21. The second most common involvement was that of a combination of the mitral and aortic valves, and there were only 5 cases of pure involvement of the aorta. One hundred and thirty-one patients developed congestive heart failure.

The time relationship between the first episode of arthritis and the development of heart failure in the patients with rheumatic heart disease was determined in 64 patients and is shown in Table IX. In most instances the time interval was less than 20 years, with a tendency to shorter time intervals.

The age at which the patients with rheumatic heart disease developed cardiac failure is illustrated in Table X. Although there is apparently a greater possibility of developing failure as the patient grows older, this complication was encountered in a high percentage of the younger patients.

Fifty-six patients with rheumatic heart disease had atrial fibrillation, an incidence of 28 per cent. Table XI shows the relationship of atrial fibrillation to heart failure. Of the 131 patients with congestive heart failure, one third had concomitant atrial fibrillation. Only 9 of the other 68 patients

Table IX. Time between first episode of arthritis and the development of heart failure

Time (yr.)	Number of patients
Less than 2	1
2-5	17
6-10	10
11-15	11
16-20	5
More than 20	20
Total	64

Table X. Age of patients with rheumatic heart disease at onset of heart failure

Age (yr.)	Total number of patients	Number of patients in failure
12-19	60	33
20-29	50	26
30-39	42	30
40-49	26	25
50-59	15	12
60 or more	6	5
Total	199	131

Table XI Relationship of atrial fibrillation to heart failure in patients with rheumatic heart disease

	Number of patients	Atrial fibrillation
With failure	131	47
Without failure	68	9
Total	199	56

Table XII Alterations in electrocardiograms of 199 patients with rheumatic heart disease

Type of alteration	Number of patients
Nonspecific changes	19
Left bundle branch block	3
Right bundle branch block	11
P mitrale	51
Right ventricular hypertrophy	25
Left ventricular hypertrophy	47
Pericarditis	12
First degree A V block	23
Premature ventricular beats	21
Premature atrial beats	6
S-T changes	10
Atrial fibrillation	56
T-wave changes	15
WPW syndrome	1

ithout failure showed this abnormality onversely of a total of 56 patients with brillation 47 had an associated conges- ve heart failure

The electrocardiographic alterations und in the patients with rheumatic heart isease are presented in Table XII

Complications of rheumatic heart disease icluded congestive heart failure in 131 trial fibrillation in 56 subacute bacterial ndocarditis in 9 and emboli in 26 patients. 'ulmonary emboli were found in 11 pa ents cerebral emboli in 10 and peripheral mboli in 4 and both cerebral and pul ionary emboli occurred in another patient 'ifteen of the patients with embolism had oncurrent atrial fibrillation. Pleural ef ision occurred in 18 patients concomit ntly with either congestive heart failure r pulmonary infarction The onset of con estive heart failure occurred during preg ancy in 32 patients

Thirty two patients with rheumatic heart disease died One patient died of acute renal insufficiency secondary to intractable shock after a prolonged period of atrial flutter one of subacute bacterial endocarditis 6 of embolism and the others died of congestive heart failure. Twenty two of the patients who died had involvement of the mitral valve alone, 9 had damage of both mitral and aortic valves and one had disease of the aortic valve only Atrial fibrillation occurred in 21 of the 32 patients who died

Discussion

The tropical condition of the island of Puerto Rico does not protect its inhabitants from developing rheumatic fever and rheumatic heart disease The series of 300 patients with rheumatic heart disease reported upon in this paper constitutes about 3 8 per cent of the total admissions to the medical department of a hospital which offers services to the indigent patients in San Juan It is our belief that the incidence of the disease is higher because in this study we have not included patients who were younger than 12 years of age nor the private patients of the community

The disease was most frequently encountered in females which agrees with the findings of other investigators. No significant racial predisposition was encountered in our study Although rheumatic fever typically has its onset in the younger age group we have some instances in which the condition was acquired in the older decades of life This is rare and it is in agreement with the experience of other observers of this illness. The most frequent manifestation was involvement of the joints, mainly as arthritis of the migratory type polyarticular and it usually started in the weight-bearing joints of the lower extremities. In some instances the involvement was manifested exclusively by pains in the joints without clinically recognizable localized articular inflammatory changes.

The arthritis occurred more frequently in the spring and winter and least frequently in the autumn which coincides with the seasonal variation reported in temperate climates. It is very difficult for us to explain the seasonal variation since in our country there are no significant climatic alterations in the seasons which

predispose to upper respiratory illnesses as postulated in the temperate zones.[14] The onset of the first episode of arthritis occurred more frequently in the second decade of life which differs somewhat from what has been reported in other centers, but the lack of study of pediatric patients in our series might partially account for this. About 8 per cent of our patients had chorea.

Skin lesions occurred in a low percentage of the patients. This is the usual experience with adult patients who develop rheumatic fever and rheumatic heart disease. Fever was very common especially in the patients who were seen with acute rheumatic fever and in those with rheumatic heart disease who had evidence of activity. The fever was of variable intensity and duration but usually responded quite dramatically to the administration of salicylates or steroids. Symptoms which could be attributed to cardiac involvement were not so prominent in our patients with acute rheumatic fever but as expected were more frequently encountered in those who came to us with evidence of established rheumatic heart disease. Hemoptysis occurred roughly in one sixth of the patients of our whole series, but mainly so in the patients with rheumatic heart disease. It occurred in association with congestive heart failure pulmonary emboli or rupture of the bronchial varices in patients with mitral stenosis.

Beta hemolytic streptococci were cultured in most of those patients with acute rheumatic fever on whom cultures were obtained. Leukocytosis occurred in only one half of these patients but the C reactive protein was significantly elevated in most of those patients in whom the test was performed. We found a low incidence of electrocardiographic abnormalities in the patients with acute rheumatic fever and we believe that this can probably be explained by the fact that a high percentage of the patients reached the hospital after they had been ill for some days and had received some treatment outside the hospital and by the fact that in some instances serial electrocardiograms were not recorded. Most of the patients who were admitted with valvular rheumatic heart disease had some evidence of activity. This emphasizes the need for prophylactic therapy in patients who have either acute rheumatic fever or active heart disease.

The disease had a predilection for the involvement of the mitral valve either alone or in combination with other valvular damage. One sixth of the patients with rheumatic heart disease died and two thirds of them had developed congestive heart failure. As recorded by other observers, the increase in the cardiac load associated with pregnancy was a contributing factor in precipitating heart failure. The most frequently encountered arrhythmia was atrial fibrillation and its presence was apparently another contributing factor in the development of congestive heart failure and in the development of peripheral and cerebral embolism.

The manifestations of rheumatic fever in Puerto Rico with regard to involvement of the joints and cardiac involvement and complications are similar to those reported in the temperate zones. We have not encountered the hyperacute strikingly severe manifestations described in some parts of the world. The presence of this illness with such a frequency in tropical areas makes us believe that the climatologic conditions are not a significant factor in the pathogenesis of this illness. Although seasonal differences similar to those in the temperate zones were noted in our patients we are under the impression that this is not a contributing factor in Puerto Rico because there are no significant alterations in temperature, rainfall and relative humidity during the different seasons of the year. It is our belief that most likely the presence of streptococcal infection in susceptible patients of poor economic condition and poor nutrition who have lowered body defenses, may constitute a higher risk for the development of the illness. The fact that two thirds of our patients came to the hospital with rheumatic heart disease points to the relative danger of the illness and again emphasizes the need for early recognition and adequate treatment of the episodes of acute rheumatic fever so as to avoid unnecessary cardiac crippling and complications years later. The transfer of patients from temperate zones to tropical areas in an attempt to improve or alter the progress of rheumatic fever or its complications is apparently unjustified.

Summary

Three hundred adult patients with rheumatic fever and/or rheumatic heart disease who were residents of a tropical zone without significant climatic alterations during the year were analyzed. This constituted 3.8 per cent of the total number of admissions to a charity hospital for a period of 8 years. Observations with regard to incidence, pathogenesis, clinical picture, and morbidity were presented. The manifestations of rheumatic fever and rheumatic heart disease in the indigent population of the tropical area of San Juan were not strikingly different from those reported in the temperate zones.

REFERENCES

1. Paul, J. R., and Dixon, G. L.: Climate and rheumatic heart disease, J.A.M.A. 108:2096, 1937.
2. Nichol, E. S.: Geographic distribution of rheumatic fever and rheumatic heart disease in the United States, J. Lab. & Clin. Med. 21:588, 1936.
3. Holbrook, W. P.: The Army Air Forces rheumatic fever control program, J.A.M.A. 126:84, 1944.
4. Coburn, A. F.: The factor of infection in the rheumatic state, Baltimore, 1931, Williams & Wilkins Company.
5. Suárez, R. M.: The incidence of heart disease in Puerto Rico, Am. Heart J. 29:439, 1945.
6. Francisco, R.: Rheumatic heart disease in the tropics, with special reference to its incidence in Puerto Rico, Clinics 5:971, 1946.
7. U. S. Department of Commerce, Weather Bureau: Local climatological data, San Juan, Puerto Rico, 1959.
8. Friedberg, C. K.: Diseases of the heart, ed. 2, Philadelphia, 1956, W. B. Saunders Company.
9. Luisada, A. A.: Heart, ed. 2, Baltimore, 1954, Williams & Wilkins Company.
10. Goldberger, E.: Heart disease, ed. 2, Philadelphia, 1955, Lea & Febiger.
11. Massey, F. C.: Clinical cardiology, Baltimore, 1953, Williams & Wilkins Company.
12. Rutstein, D. B., et al.: Jones criteria (modified) for guidance in the diagnosis of rheumatic fever, Circulation 13:617, 1956.
13. Nomenclature and criteria for diagnosis of diseases of the heart and blood vessels, New York Heart Association, Inc., 1953.
14. Rammelkamp, C. H., Wannamaker, L. W., and Denny, F. W.: The epidemiology and prevention of rheumatic fever, Bull. New York Acad. Med. 28:321, 1952.

The vectorcardiogram in ventricular septal defect associated with pulmonary stenosis
A study of 60 cases

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References are found in publications which analyze congenital heart diseases and ventricular enlargements in general[1-4] but few vectorcardiographic studies have been made of ventricular septal defect (VSD) associated with pulmonary stenosis (PS). Hemodynamically, we can divide the cases of VSD with PS into two main groups[5,6]: *Group 1—VSD plus PS with predominant venoarterial shunt.* These patients are cyanotic, the pulmonary circulation is diminished, and the left ventricle is anatomically normal. This group includes the cases of tetralogy of Fallot. These patients, when they have undergone previously a shunt operation, may show a diminution of cyanosis and an enlarged left ventricle on x-ray examination. *Group 2—VSD plus PS with predominant arteriovenous shunt.* These patients are noncyanotic with normal or slightly increased pulmonary circulation and anatomic enlargement of the left ventricle.

In the present study, we tried to investigate the behavior of the vectorcardiogram in these different situations.

Material and methods

The diagnosis was made by means of clinical and hemodynamic data, and was confirmed in all patients by open-heart operation. From the clinical and hemodynamic points of view, our material was divided in two groups. *Group 1*—Cyanotic patients who had VSD plus PS with venoarterial shunt (53 patients). In all cases the pulmonary stenosis was of the infundibular valvular type. In 11 patients there was a previous surgical shunt (aortopulmonary) which, however, was in good function only in 6 patients. One of the patients had patent ductus arteriosus with aortopulmonary shunt. *Group 2*—Noncyanotic patients who had VSD plus PS with arteriovenous shunt (7 patients). The pulmonary stenosis was of the valvular type.

For the taking of the vectorcardiograms we used Grishman's cube method, and in all cases the light was modulated and interrupted 400 times per second.

Results

Group 1 (53 patients). According to the rotation in the horizontal plane (HP), the vectorcardiograms of this group were divided into three subgroups.

A. HP WITH CLOCKWISE ROTATION IN THE WHOLE EXTENSION OF THE LOOP ... TIENTS (Fig. 1). In Table I ...

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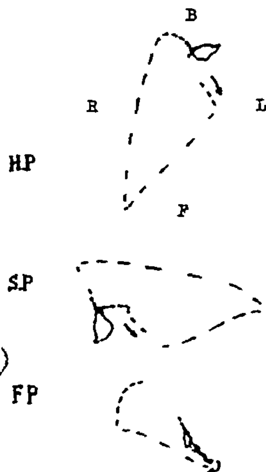


Fig. 1. VSD plus PS with enoarterial shunt. Note the angle with concavity of the initial portions pointing to the left in the horizontal plane (*H.P.*). *S.P.* Sagittal plane. *F.P.* Frontal plane.

established among the radiologic data, rotations of the QRS loop in the different planes, and the orientation of TsÊ. In 6 patients it is seen that important portions of the QRS loop were directed upward, backward, and to the right. Five patients had the Blalock shunt, and one had patent ductus arteriosus (PDA).

Of all the patients who underwent a Blalock anastomosis, only 2 showed functioning of the artificial shunt, and both had biventricular enlargement on x-ray examination. Two of the 3 patients whose vectorcardiograms showed counterclockwise rotation in the frontal plane (FP) (Fig. 2) had left ventricular enlargement on x-ray examination.

In the other patients the rotation was clockwise in 23 and figure of eight in the rest. In the sagittal plane (SP), the rotation was predominantly counterclockwise or figure of eight, and in only 2 patients was the loop directed clockwise (both with counterclockwise rotation in the frontal plane). In all cases the TsÊ was directed downward and to the left, backward in 15 and forward in 17.

B. HP WITH PREDOMINANT CLOCKWISE ROTATION BUT WITH PRETERMINAL COUNTERCLOCKWISE APPENDIX (18 PATIENTS) (Table II, Fig. 3). The preterminal appendix showed a duration that varied from 0.01 to 0.03 second (Table II). In 7 cases, terminal delay was also registered. Three patients showed a previous shunt, and in the only patient with a functioning shunt the left ventricle was enlarged on x-ray examination. The QRS loop showed a counterclockwise rotation in the frontal plane in one patient. In the other patients the rotation was either clockwise or in a figure-of-eight form (Table II). The QRS loop showed a clockwise rotation in the sagittal

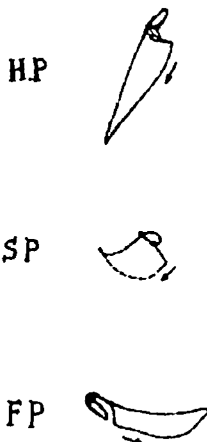


Fig. 2. VSD plus PS with Blalock-Taussig shunt. X-ray examination showed combined ventricular enlargement. Notice the counterclockwise rotation in the frontal plane (*F.P.*).

plane in only one patient and in the others it was either counterclockwise or in a figure-of-eight form. In all cases the TsÊ was directed backward, downward, and to the left.

C. HP WITH COUNTERCLOCKWISE ROTATION OR FIGURE-OF-EIGHT INSCRIPTION (3 PATIENTS) (Fig. 4). All of the patients had undergone a Potts operation and the anastomosis was functioning. Table III shows the correlations between the radiologic data and the rotation of the QRS loop in the different planes.

The vectorcardiograms with counterclockwise rotation in the horizontal plane showed great magnitude and forward and rightward orientation in the first 0.02 second (Fig. 4). In all 3 patients the TsÊ was directed forward, downward, and to the left, and a biventricular overloading was present on x-ray examination (Table III).

Studying the initial 0.02 second of the QRS loop in the subgroups A and B (50 patients), we observed that in 2 patients of subgroup A this portion was of important magnitude and was directed to the left (Fig. 5). In the other 48 patients this initial portion showed a peculiar behavior, namely: (1) Cases with initial portions (0.01 to 0.015 second) directed forward and to the right, followed by a small portion oriented to the left, with a duration equal to or less than 0.01 second. Because of this fact, an angle with its concavity facing left was formed (20 patients) (Fig.

Table I

Patient number	*X-ray findings*		*Rotation*		*Surgical shunt*
	Right ventricle	*Left ventricle*	*Sagittal plane*	*Frontal plane*	
1	++	–	Figure of eight	C	
2.	++	–	CC	C	
3	++	–	CC	C	
4.	++	–	Figure of eight	C	
5	++	–	CC	C	
6.	++	+	C	CC	Blalock functioning
7	++	–	Figure of eight	C	
8.	++	++	Figure of eight	CC	Blalock functioning
9	++	–	Figure of eight	C	
10.	+++	+++	CC	C	PDA
11.	++	–	CC	C	Blalock not functioning
12.	+++	–	CC	C	Blalock not functioning
13.	++	–	CC	C	
14.	++	–	CC	C	
15.	++	–	CC	C	
16.	++	–	Figure of eight	C	
17	++	–	Figure of eight	C	
18.	++	–	Figure of eight	C	
19	+	–	Figure of eight	Figure of eight	
20.	+	–	CC	C	
21	++	–	CC	C	
22.	++	–	Figure of eight	C	
23.	++	–	Figure of eight	C	
24	++	–	CC	C	
25	++	–	Figure of eight	Figure of eight	
26.	++	–	Figure of eight	Figure of eight	
27	+++	–	Figure of eight	Figure of eight	
28.	++	–	Figure of eight	C	
29	++	–	Figure of eight	C	
30	+	–	CC	C	
31	++	–	Figure of eight	C	
32.	++	–	CC	C	Blalock not functioning

C: Clockwise. CC: Counterclockwise. PDA: Patent ductus arteriosus.

Table II

Patient number	X-ray findings		Rotations		Preterminal appendix duration (sec)	Surgical shunt
	Right ventricle	Left ventricle	Sagittal plane	Frontal plane		
33.	++	–	CC	C	0 015	Potts not functioning
34	++	–	Figure of eight	C	0 020	
35	+++	–	Figure of eight	Figure of eight	0 020	
36.	+++	–	Figure of eight	C	0 030	
37	++	–	CC	C	0 015	
38.	+	–	Figure of eight	Figure of eight	0 010	
39	+	–	CC	C	0 010	
40	++	–	CC	C	0 015	Blalock not functioning
41	+++	–	CC	C	0 010	
42.	+++	–	Figure of eight	Figure of eight	0 010	
43	++	–	Figure of eight	Figure of eight	0 020	
44	++	++	Figure of eight	CC	0 015	Blalock functioning
45	+	–	Figure of eight	Figure of eight	0 010	
46	++	–	Figure of eight	C	0 010	
47	++	–	C	Figure of eight	0 010	
48.	+	–	Figure of eight	C	0 020	
49	++	–	Figure of eight	Figure of eight	0 015	
50	++	–	Figure of eight	Figure of eight	0 030	

Table III

Patient number	X-ray findings		Rotations		
	Right ventricle	Left ventricle	Horizontal plane	Sagittal plane	Frontal plane
51	++	+++	CC	C	Figure of eight
52.	+++	++	Figure of eight	Figure of eight	C
53.	++	+++	CC	C	C

1) (2) Cases with the first portion of small magnitude tending to be directed leftward and forward or backward forming with the rest of the loop a convexity facing left (22 patients) (Fig 6) (3) Cases with no angulation whatsoever since the initial portions of the loop were oriented directly forward and to the right thus forming a straight line that continued with the rest of the curve (6 patients) (Fig 7)

Group 2 (7 cases) Rotation of the QRS loop in different planes and its relationship to the radiologic ventricular enlargement are analyzed in Table IV It is interesting to note that 2 of 3 patients with clockwise rotation in the horizontal plane showed portions of certain magnitude directed to the left (Fig 8) Two of the 3 patients with counterclockwise rotation in the horizontal plane showed an initial 0.02 second of great magnitude and directed to the right and forward One patient presented important preterminal and terminal slowing

Analysis of Table IV indicates that counterclockwise rotation in the frontal plane occurred in 72 per cent of the patients (Fig 8) In every one of these patients there was left ventricular enlargement from the radiologic point of view

Discussion

From the vectorcardiographic and radiologic points of view our material can be divided into the following groups

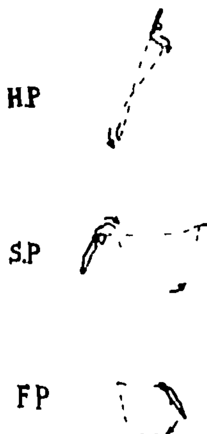


Fig. 3 VSD plus PS with venoarterial shunt. The horizontal QRS loop presents a preterminal appendix of 0.010 second duration and counterclockwise inscription.

1 *VSD plus PS with right ventricular overloading* (*47 patients*). Because of the extent of pulmonary stenosis in these patients, only the right ventricle showed enlargement on x-ray examination. Analysis of the cardiac catheterization data in these patients reveals similar systolic pressures in the two ventricles (the so-called systemic right ventricle). Our material permits us to establish the vectorcardiographic elements which characterize this hemodynamic condition (83 per cent of the cases). They are as follows: in the horizontal plane the initial portion (0.01 or 0.015 second) is oriented forward and to the right, followed by a small portion oriented to the left with a duration equal to or shorter than 0.01 second, thus forming an angulation with its concavity facing left (40 per cent of the cases) (Figs. 1-3). In the other cases the initial portion of small magnitude was oriented leftward (either forward or backward) forming with the rest of the loop a convexity facing left (43 per cent) (Fig. 6) and there was clockwise rotation in the whole extension of the QRS loop or a counterclockwise preterminal appendix. Cabrera[7] admits that this counterclockwise appendix is more frequent in those cardiopathies in which the systolic pressure is higher in the right ventricle than in the left, although this is not in agreement with our experience. The TsÊ is directed forward or backward, downward and to the left, but never upward. In spite of the hemodynamic condition in the other 8 patients the vectorcardiographic behavior in 6 cases was like that in cardiopathies in which the right ventricular systolic pressure surpasses the systemic pressure, that is, the QRS loop spins clockwise in the horizontal plane and

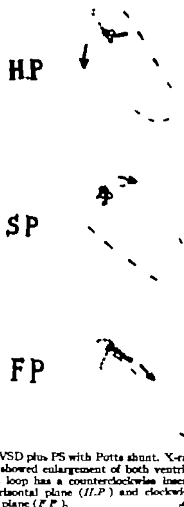


Fig. 4 VSD plus PS with Potts shunt. X-ray examination showed enlargement of both ventricles. The QRSsÊ loop has a counterclockwise inscription of the horizontal plane (*H.P.*) and clockwise of frontal plane (*F.P.*).



Fig 5 VSD plus PS with venoarterial shunt Initial 0.02-second forces of important magnitude are directed to the left.

is directed completely forward and to the right (Fig 7) In 2 patients the vectorcardiogram behaved as though the right ventricular systolic pressure were lower than the systemic pressure that is the QRS loop showed a clockwise rotation in the horizontal plane with important portions oriented to the left (Fig 5)

2 *VSD with right ventricular overloading (RVO) associated with right bundle branch block (RBBB)* In these peculiar cases, the diagnosis of RVO in the presence of RBBB is rendered difficult especially when the conduction disturbance is severe. This fact is explainable to a certain extent, since in both conditions there are important forces oriented forward and to the right

From the vectorcardiographic point of view RBBB shows two different morphologies in the horizontal plane (a) The horizontal QRS loop is directed counterclockwise in its whole extension with a delayed preterminal appendix oriented forward and to the right. When this aspect is present, the diagnosis of associated RVO is very difficult (b) The horizontal QRS loop shows a clockwise spin in its initial portions and a counterclockwise delayed preterminal appendix. The above-described pattern is seen in many congenital cardiopathies with RVO (18 of our patients) (Fig 9 Table II)

Cabrera and associates[3] admit that in such cases the mere presence of the preterminal appendix is sufficient to make the diagnosis of associated RBBB

In our experience which is based principally on the RBBB that appears after the surgical correction of tetralogy of Fallot and isolated infundibular pulmonary stenosis[9] the diagnosis of conduction disturbance should be made only when the preterminal appendix shows a duration of 0 015 second or more and the delay is observed in two planes (Fig 9) Right ventricular overloading is recognized by the small magnitude of the initial portions oriented to the left (Fig 9) and by the clockwise rotation of the QRS loop in the

Table IV

Patient number	*X-ray findings*		*Rotations*		
	Right ventricle	*Left ventricle*	*Horizontal plane*	*Sagittal plane*	*Frontal plane*
54	++	++	CC	CC	CC
55	++	+	C	Figure of eight	CC
56.	+++	++	C	CC	CC
57	+	++	CC	CC	CC
58.	++	+	Figure of eight	Figure of eight	CC
59	++	++	CC	Figure of eight	C
60.	+	++	C	CC	Figure of eight

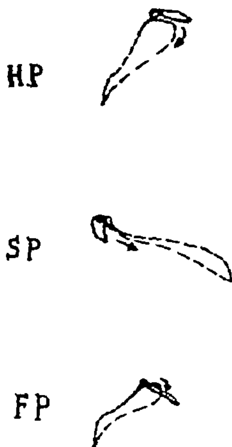


Fig 4 VSD plus PS plus patent ductus arteriosus with aortopulmonary shunt The initial portion of the QRS loop shows a convexity oriented to the left. Note the terminal delay in the QRS loop.

frontal plane and counterclockwise rotation in the sagittal plane. In the cases in which the preterminal appendix lasts less than 0 01 second we do not make the diagnosis of associated conduction disturbance since this appendix usually disappears with respiratory movements and is not found in the frontal and sagittal planes.

3 *VSD plus PS with biventricular overloading* In 14 patient who had enlargement of both ventricles on x-ray examination 13 showed biventricular overloading in the vectorcardiogram The left ventricular enlargement is due to a volumetric overloading related to the arteriovenous shunt through the VSD (in some cases (Table IV) and to the increase in the diastolic volume through a surgical shunt in other cases (Tables I III) Vectorcardiographically these cases can be divided as follows

A. PATIENTS WITH PREDOMINANT VSD OR AORTOPULMONARY SHUNT (POTTS TYPE) The QRS loop in the horizontal plane showed counterclockwise rotation or clockwise rotation but with the initial portion of a certain magnitude oriented to the left The diagnosis of biventricular overloading could be made on the basis of the following data

When the rotation is counterclockwise in the horizontal plane (Fig 4) RVO is suspected because of an initial portion of great magnitude which is directed forward and to the right This diagnosis is confirmed by the clockwise rotation of the QRS loop in the frontal plane (Fig 4) in 60 per cent of our cases.

If the QRS loop shows clockwise rotation in the horizontal plane (Fig 8) the diagnosis of left ventricular overloading (LVO) is made by the counterclockwise rotation

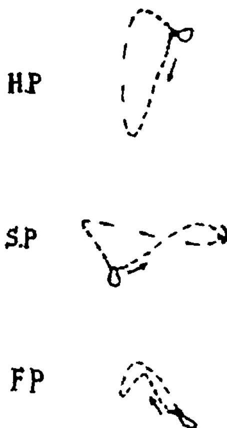


Fig 7 VSD plus PS with venoarterial shunt. The initial portion of the QRS loop in the horizontal plane (H.P) is oriented anteriorly and to the right depicting a straight line that continues of the curve

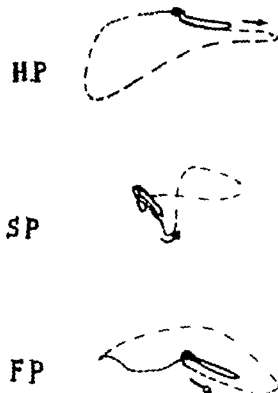


Fig. 8 VSD plus PS with arteriovenous shunt. X-ray examination revealed enlargement of both ventricles. The QRSsÊ loop shows a clockwise inscription in the horizontal plane and counterclockwise in the frontal plane. Note portions of certain magnitude directed to the left

in the frontal plane and by important portions of the loop directed to the left (Fig 8) LVO therefore disfigures the vectorcardiographic image in such a way that the vectorcardiogram does not show the characteristics found in cases of systemic right ventricle but rather those observed in congenital cardiopathies with arteriovenous shunt without severe pulmonary hypertension

B. PATIENTS WITH PREDOMINANT PS IN SPITE OF AN ARTERIOVENOUS SHUNT (BLALOCK TYPE) The vectorcardiogram in the horizontal plane possesses the same characteristics as those described for Group 1 (Fig 2) and the diagnosis of LVO is made by the counterclockwise rotation of the QRS loop in the frontal plane. The vectorcardiographic modification caused by the shunt was much greater in the patients in whom a Potts anastomosis was made. This fact can be somehow explained by the caliber of the two vessels and by the diameter of the surgical fistula. It should be stated that in only one of our patients was the QRS loop (with counterclockwise rotation in the frontal plane and clockwise rotation in the horizontal plane) not accompanied by associated left ventricular enlargement. In another patient (Fig 6) although the x-ray examination revealed left ventricular enlargement this could not be diagnosed by vectorcardiography. We believe that this fact is due in part to the presence of an important terminal delay associated with RVO

Summary

We have analyzed the vectorcardiographic behavior in 60 cases of ventricular septal defect plus pulmonary stenosis (VSD plus PS). We have discussed the criteria for the recognition of the so-called systemic right ventricle biventricular overloading and right bundle branch block associated with right ventricular overload and we have emphasized the different be-

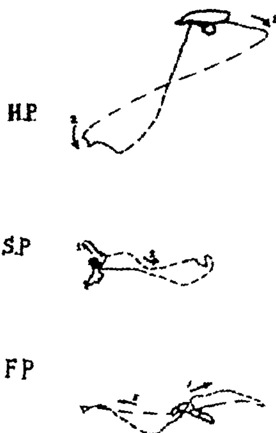


Fig. 9 VSD plus PS with arterial shunts. The horizontal QRS loop presents a preterminal appendix of 0.020 second and counterclockwise inscription

havior of the vectorcardiogram in the cases of VSD plus PS with venoarterial and arteriovenous shunt.

REFERENCES

1. Lasser R. P., Borun, E. R., and Grishman, A. Spatial vectorcardiography. Right ventricular hypertrophy as seen in congenital heart disease, Am. Heart J 42:370, 1951
2. Donoso E., Sapin S., Braunwald, E., and Grishman, A. A study of the electrocardiogram and vectorcardiogram in congenital heart disease. II Vectorcardiographic criteria for ventricular hypertrophy. Am. Heart J 50:674 1955
3. Dack, S. The electrocardiogram and vectorcardiogram in ventricular septal defect, Am J Cardiol. 5:199 1960.
4. Bergovich, J Bleifer S., Donoso E., and Grishman, A. Vectorcardiogram and electrocardiogram in ventricular septal defect, with special reference to the diagnosis of combined ventricular hypertrophy. Brit. Heart J 12:205 1960.
5. Gasul, B M., Dillon, R. F and Urla, V. Ventricular septal defects. Their natural transformation into those with infundibular stenosis or into the cyanotic or noncyanotic type of tetralogy of Fallot, J.A.M.A. 164:847 1957
6. Rowe, R. D Vlad, P., and Keith, J D. Atypical tetralogy of Fallot. a noncyanotic form with increased lung vascularity. Circulation 12:230 1955
7. Cabrera, E. Personal communication.
8. Cabrera, E., Gaxiola, A., Eisenberg P and Smoler J La ectocardiografia para el cardiologo. Part II Principia cardiológica 4 189 1957
9. Pileggi, F Ebaid M., Tranchesi, J Delmonte, B., Jatene, A and Décourt, L. V The vectorcardiogram in complete right bundle branch block after surgery with extracorporeal circulation, Abstracts of the Sixth Interamerican Congress of Cardiology 1:54 1960.

Clinical evaluation of an improved direct-writing phonocardiograph

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In an earlier report from this laboratory we suggested that a direct-writing phonocardiograph with adequate dynamic characteristics should significantly increase the clinical utility of the registration of heart sounds.[1] Although an instrument with inadequate response capabilities was employed in the study, the results offered considerable promise for further technical development and clinical application. Further analysis indicated that the dynamic characteristics of available direct-writing electrocardiographic galvanometers might be improved sufficiently to render them adequate for phonocardiographic use.

The design principles which were set forth in the earlier study have since been applied to the development and construction of a direct-writing phonocardiograph with much better fidelity of registration than the equipment which we originally employed. The present communication will describe some of the constructional features and operational characteristics of the newer instrument. However, the major portion of this report will be devoted to a consideration of the clinical adequacy of the instrument as evaluated by comparison with an instrument employing conventional optical registration.

Technical aspects of the new instrument

A dual-channel direct-writing galvanometer assembly was manufactured for us.† One of the galvanometers was similar to that which the Burdick Corporation uses in their EK III electrocardiograph. The other galvanometer was specially constructed to meet the design considerations which are necessary for operation at high frequency. The styluses of both galvanometers were of the heated type which inscribe directly on conventional single-channel electrocardiograph paper. Paper speeds of 25 and 50 mm. per second were provided by the drive mechanism.

The specially constructed galvanometer (phonogalvanometer) had a natural frequency of 117 cycles per second. In order to compensate for the reduced amplitude of deflection which occurs when a correctly damped galvanometer is driven at or beyond its natural frequency, we designed and constructed an equalizer-amplifier with highly flexible control over the form of its frequency-response characteristics. With the frequency-compensating controls properly adjusted, the over-all frequency response curve of the phonogalvanometer was essentially flat from 20 to beyond 400

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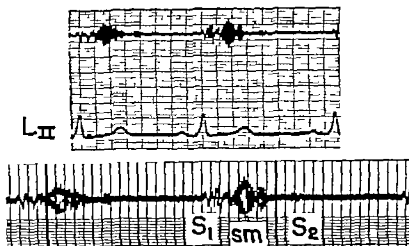


Fig 1 Simultaneous comparative tracings of a low-pitched musical murmur which has a peak fundamental frequency of approximately 110 cycles per second. *Upper strip* Direct sound and Lead II registration at 50 mm per second. *Lower strip*. Optical registration at 75 mm. per second Recorded at stethoscopic setting from the apex of the heart of a patient with rheumatic aortic stenosis. Both tracings show the first and second sounds (S_1 and S_2, respectively), and a diamond-shaped systolic murmur (*sm*). Because the vibrational frequency of the murmur is almost the same as the natural frequency of the galvanometer phase lag in the upper strip is only about 2 milliseconds. The fact that the murmur is musical and so well transmitted toward the apex suggests that the entire aortic valvular structure is vibrating as a unit in piston like fashion (Gallavardin's phenomenon). Further discussion in text

cycles per second In accordance with the results of our previous design analysis,[1] we operated the phonogalvanometer at approximately 65 per cent of critical damping

As was the case in our original study we employed the Sanborn dynamic (electromagnetic) cardiac microphone and optical galvanometer recorder The amplified microphone signal was tapped from the audiophone monitoring stage of the Sanborn instrument and introduced into the input of the equalizer-amplifier thus permitting simultaneous optical and directly inscribed registration of heart sounds. At the same time the other galvanometer of the special Burdick assembly was employed to record an electrocardiographic signal usually Lead II

So-called stethoscopic registration was obtained with the direct writer when the over-all frequency-response curve was adjusted to the flat form described above To obtain so-called logarithmic (or "ear like") records, one of the frequency controls was turned to a previously determined position at which the slope of the frequency-response curve was +3 decibels per octave increase between 20 and 400 cycles per second

Results

Optically and directly inscribed phonocardiograms were recorded simultaneously from 30 subjects with auscultatory abnormalities The photographic tracings were recorded at a paper speed of 75 mm per second and the directly inscribed tracings at 50 mm per second Simultaneous photographic registration of the electrocardiographic lead was omitted The recording routine consisted of both stethoscopic and logarithmic registration from (a) the apical region of the precordium (b) the mid-precordium (c) the fourth intercostal space along the left sternal margin (tricuspid area) (d) the second intercostal space along the right sternal margin (aortic auscultatory area) and (e) the second intercostal space along the left sternal margin (pulmonic area) Rou

*Sanborn Twin Beam recorder with No. 62 300 phonoamplifier and No. 62-1500 cardiac microphone, Sanborn Company Waltham, Mass.

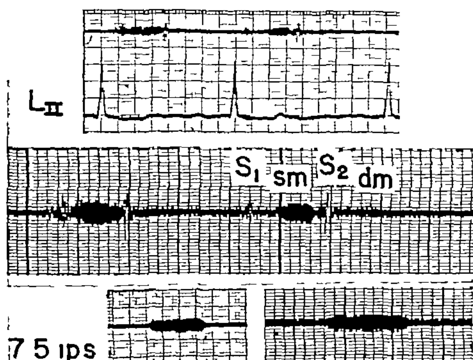


Fig 2 Simultaneous direct (*upper strip*) and optical (*middle strip*) registration of a high-pitched musical murmur (*sm*). The fundamental vibrational frequency of the murmur is 435 cycles per second, with a strong harmonic component at double that frequency Recorded from the auscultatory aortic area of a 25-year-old female patient with chronic rheumatic valvular disease. An aortic diastolic murmur (*dm*) is also present, as well as the first and second heart sounds. The murmur was also recorded on magnetic tape at 15 inches per second and then played back at half speed simultaneously into the direct writer (*left panel lower strip*) and the optical recorder (*right panel lower strip*). This intermediate recording procedure doubles the effective paper speed and significantly extends the response capabilities of both types of instrument Further discussion in text

tinely the large or medium-sized microphone bell was used according to the size and bony structure of the chest Additional recording techniques were employed when indicated such as registration at the apex with the patient in the left lateral decubitus position in cases of mitral stenosis and the use of a diaphragm chest piece in patients with faint diastolic murmurs at the base of the heart

Careful inspection of the simultaneously recorded phonocardiograms shows that the direct writer produces tracings which compare rather favorably in quality and diagnostic content with the photographic tracings. As expected we found the optical galvanometer capable of producing sharper tracings than the direct writer Apparently this is related to a tendency for excessive transfer of heat from the hot stylus (flooding) for relatively small deflection velocities, and inadequate transfer of heat (skipping) for relatively rapid deflections. Very careful adjustment of the heat pressure and alignment of the stylus was found to minimize these defects but they could not be eliminated altogether It seems likely that flooding from the stylus might be further reduced by registration at increased paper speed but we have not yet investigated this possibility

In general the new instrument was found to record heart-sound transients with clinically acceptable accuracy The form of the major deflections was well preserved including most of the notches and slurs observed in the photographic records. Only very small notches and highly subtle inflections were lost in the directly inscribed tracings. The relative position of a given notch in the deflection upon which it was superimposed differed very little in the comparative tracings. We interpret this observation as an indication that dis-

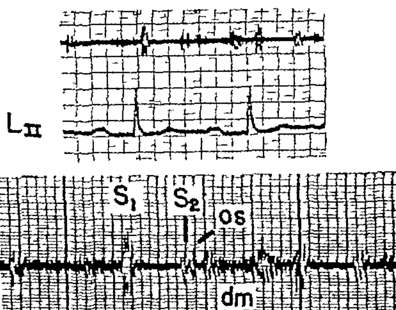


Fig. 3. Stethoscopic registration from the apex of a 27-year-old Negro woman with mitral stenosis. The simultaneously recorded strips are *upper* direct writer at 50 mm. per second, *lower* optical recorder at 75 mm. per second. The tracings show a snapping first sound (S_1), a short, soft early systolic murmur (not labeled), and a split second sound which somewhat erroneously is labeled S_2—os. An opening snap which occurs approximately 0.10 second after the onset of the first component of the split second sound ushers in a characteristic rumbling diastolic murmur, *dm*. In this case the accentuated portion of the diastolic rumble is well separated from the first heart sound because of the first-degree atrioventricular block (P-R interval of 0.28 second). Further discussion in text.

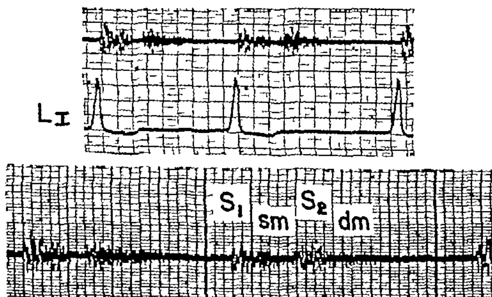


Fig. 4. Comparative direct and optical phonocardiograms recorded from the cardiac base of a patient with syphilitic aortic valvular disease. The tracings show the first and second heart sounds (S_1 and S_2, respectively), a *systolic murmur* (*sm*), and the characteristic decrescendo diastolic murmur (*dm*) of aortic valvular insufficiency. The direct writer (*upper strip*) displays the [illegible] with clinically adequate fidelity [illegible] the inherent mechanical limitations of [illegible] Further discussion in text.

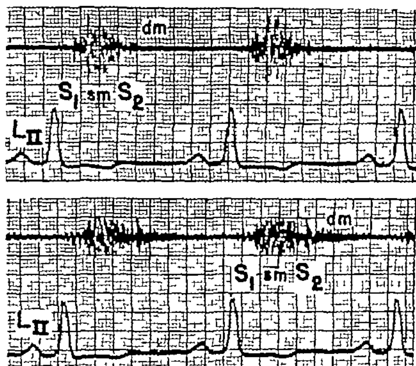


Fig 5 Phonocardiograms recorded by the direct writer from the cardiac base of a patient with chronic rheumatic aortic valvular disease The upper strip shows the first and second heart sounds (S_1 and S_2, respectively), a very intense aortic systolic murmur (*sm*) and a very soft barely perceptible aortic diastolic murmur (*dm*). The lower strip was recorded immediately after the upper strip, with the sensitivity of the instrument increased several fold but with the stylus and galvanometer coil protected by an electronic limiting device. The increased sensitivity permits registration of the diastolic murmur with adequate amplitude of deflection (*dm* in the lower strip). The lower strip also shows "clipping" of the systolic murmur and the second sound due to the protective action of the limiting circuit.

tortion due to phase lag is much less significant than we had originally feared A related desirable feature of the direct writer is its capability of displaying abrupt onset of sonic energy such as that which characterizes the snappy quality of the first heart sound in mitral stenosis.

Apart from the obvious consideration of loudness, the ability of the direct writer to record murmurs accurately is related to the quality and predominant pitch or frequency of the murmur As had been anticipated musical murmurs tended to be recorded with great accuracy (Fig 1) because the sound vibrations are of simple sinusoidal form and largely without abrupt changes in amplitude and frequency In virtually all cases the fundamental frequency of musical murmurs can be expected to fall well within the dynamic range capabilities of the new instrument

The most demanding example of a musical murmur which we encountered is illustrated in Fig 2 The subject was a 25-year-old white woman with a loud high pitched musical murmur due to aortic valvular stenosis of rheumatic etiology By photographing the amplified signal from the face of a cathode-ray oscilloscope we determined that the fundamental frequency of the sound was 435 cycles per second with a strong harmonic component at 870 cycles per second The comparative tracings (upper two strips of Fig 2) show that the direct writer was capable of displaying this unusually high-pitched musical sound in a clinically adequate manner even though virtually none of the strong harmonic component is represented in the deflections.

In nonmusical murmurs there tends to be a random distribution of frequencies.

However, there is also a tendency for some particular frequency to predominate, giving the clinical auscultatory impression of so-called high pitched, medium-pitched, and low pitched nonmusical murmurs. Since the higher pitched murmurs impose greater physical demands upon the direct writer, they tend to be somewhat less accurately recorded than the lower pitched sounds. Fortunately, this difference in quality of registration does not appear to be of any special importance in so far as routine diagnostic phonocardiography is concerned (Figs. 3 and 4).

During the initial portion of this comparative study we observed that low intensity murmurs were more likely to be recorded with the optical device than with the direct writer. This was due to the fact that the optical galvanometer could be operated at increased sensitivity without harm from overdriving, whereas it was feared that the same relative amplification applied to the phonogalvanometer might damage it. Therefore, a simple electronic limiting circuit was devised which permitted operation of the phonogalvanometer at considerably increased sensitivity by clipping the energy peaks of relatively intense heart sounds. Fig. 5 illustrates the application of this limiting circuit to a subject who had a loud systolic murmur and a very soft diastolic murmur at the base of the heart. With the direct writer, as with conventional recorders, the intensity of some murmurs is so low that they cannot be recorded. It seems likely that the use of Groom's[2] low-noise capacitance microphone should improve this situation.

Discussion

Attempts at direct writing phonocardiography are not new. Both we[1] and Lawson[3] have shown that the use of a conventional electrocardiograph as a recorder is not entirely without merit, especially for the purpose of recognizing and timing heart sound transients. Lawson's scheme for such limited application is especially attractive since it requires only simple and relatively inexpensive additional equipment. Judging from some of Caniggia's published illustrations, he also has employed a form of direct inscription.[4] At the present time at least two direct writing phonocardiographs are available commercially.* Since we have not had the opportunity to compare the performance of these instruments with optical recorders, we prefer to reserve judgment on them. Another type of "direct writer" is available commercially; it uses self-developing photographic paper that is sensitive to ultraviolet light. Although the dynamic characteristics available in such recorders are excellent, they do not seem to be suitable for use at the bedside because of excessive noise from the blower which cools the source of ultraviolet light.

Although the new phonogalvanometer represents a great advance over our earlier instrument, it still suffers, at least in theory, from the difficulties that beset the "brute force" energization of recorders. Therefore it was gratifying to learn from this comparative study that these difficulties were less troublesome at the level of practical clinical application than may have been anticipated. In so far as we were able to determine, almost all of the clinically important information obtained by the optical device was also recorded by the direct writer. However, the implication that direct writing phonocardiography can or should eventually replace all other types of registration is not intended. It is our belief that much remains to be learned from the continued application of oscillographic systems with high figures of merit, and from special techniques such as spectrographic registration and analysis.

The lower strip of Fig. 2 illustrates how the use of magnetic tape as an intermediate recording modality can provide a compromise between the dynamic limitations of direct writers and the desire for increased accuracy in oscillographic registration. In essence, cardiovascular sounds can be recorded as frequency-modulated signals at high tape speed and played back into the direct writer at a lower speed. This maneuver serves the dual purpose of effectively multiplying the phonocardiographic paper speed by the ratio of the higher to the lower tape speed, and of extending the response capacity of the direct writer by essentially the same ratio. The advantages

*Elema-Schonander Mingograph Recorder (distributed in the United States by Schick X-Ray Company, Inc., Chicago, Ill.). The Schwarzer Co., Boston, Mass.

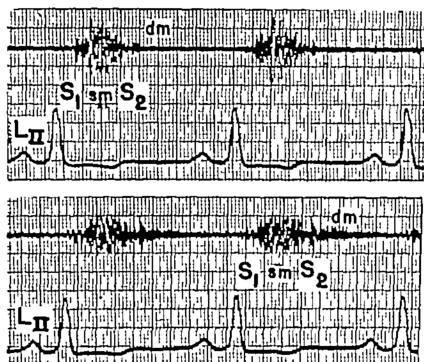


Fig. 5. Phonocardiograms recorded by the direct writer from the cardiac base of a patient with chronic rheumatic aortic valvular disease. The upper strip shows the first and second heart sounds (S_1 and S_2, respectively), a very intense aortic systolic murmur (*sm*), and a very soft, barely perceptible aortic diastolic murmur (*dm*). The lower strip was recorded immediately after the upper strip, with the sensitivity of the instrument increased several fold, but with the stylus and galvanometer coil protected by an electronic limiting device. The increased sensitivity permits registration of the diastolic murmur with adequate amplitude of deflection (*dm* in the lower strip). The lower strip also shows "clipping" of the systolic murmur and the second sound due to the protective action of the limiting circuit.

tortion due to phase lag is much less significant than we had originally feared. A related desirable feature of the direct writer is its capability of displaying abrupt onset of sonic energy, such as that which characterizes the snappy quality of the first heart sound in mitral stenosis.

Apart from the obvious consideration of loudness, the ability of the direct writer to record murmurs accurately is related to the quality and predominant pitch or frequency of the murmur. As had been anticipated, musical murmurs tended to be recorded with great accuracy (Fig. 1) because the sound vibrations are of simple sinusoidal form and largely without abrupt changes in amplitude and frequency. In virtually all cases the fundamental frequency of musical murmurs can be expected to fall well within the dynamic range capabilities of the new instrument.

The most demanding example of a musical murmur which we encountered is illustrated in Fig. 2. The subject was a 25-year-old white woman with a loud, high-pitched musical murmur due to aortic valvular stenosis of rheumatic etiology. By photographing the amplified signal from the face of a cathode-ray oscilloscope we determined that the fundamental frequency of the sound was 435 cycles per second with a strong harmonic component at 870 cycles per second. The comparative tracings (upper two strips of Fig. 2) show that the direct writer was capable of displaying this unusually high-pitched musical sound in a clinically adequate manner even though virtually none of the strong harmonic component is represented in the deflections.

In nonmusical murmurs there tends to be a random distribution of frequencies

However, there is also a tendency for some particular frequency to predominate, giving the clinical auscultatory impression of so-called high-pitched, medium-pitched, and low-pitched nonmusical murmurs. Since the higher pitched murmurs impose greater physical demands upon the direct writer, they tend to be somewhat less accurately recorded than the lower pitched sounds. Fortunately, this difference in quality of registration does not appear to be of any special importance in so far as routine diagnostic phonocardiography is concerned (Figs. 3 and 4).

During the initial portion of this comparative study, we observed that low-intensity murmurs were more likely to be recorded with the optical device than with the direct writer. This was due to the fact that the optical galvanometer could be operated at increased sensitivity without harm from overdriving, whereas it was feared that the same relative amplification applied to the phonogalvanometer might damage it. Therefore, a simple electronic limiting circuit was devised which permitted operation of the phonogalvanometer at considerably increased sensitivity by clipping the energy peaks of relatively intense heart sounds. Fig. 5 illustrates the application of this limiting circuit to a subject who had a loud systolic murmur and a very soft diastolic murmur at the base of the heart. With the direct writer, as with conventional recorders, the intensity of some murmurs is so low that they cannot be recorded. It seems likely that the use of Groom's[9] low noise capacitance microphone should improve this situation.

Discussion

Attempts at direct writing phonocardiography are not new. Both we[1] and Lawson[3] have shown that the use of a conventional electrocardiograph as a recorder is not entirely without merit, especially for the purpose of recognizing and timing heart sound transients. Lawson's scheme for such limited application is especially attractive since it requires only simple and relatively inexpensive additional equipment. Judging from some of Caniggia's published illustrations, he also has employed a form of direct inscription.[4] At the present time at least two direct-writing phonocardiographs are available commercially.* Since we have not had the opportunity to compare the performance of these instruments with optical recorders, we prefer to reserve judgment on them. Another type of "direct writer" is available commercially; it uses self-developing photographic paper that is sensitive to ultraviolet light. Although the dynamic characteristics available in such recorders are excellent, they do not seem to be suitable for use at the bedside because of excessive noise from the blower which cools the source of ultraviolet light.

Although the new phonogalvanometer represents a great advance over our earlier instrument, it still suffers, at least in theory, from the difficulties that beset the "brute force" energization of recorders. Therefore it was gratifying to learn from this comparative study that these difficulties were less troublesome at the level of practical clinical application than may have been anticipated. In so far as we were able to determine, almost all of the clinically important information obtained by the optical device was also recorded by the direct writer. However, the implication that direct-writing phonocardiographs can or should eventually replace all other types of registration is not intended. It is our belief that much remains to be learned from the continued application of oscillographic systems with high figures of merit and from special techniques, such as spectrographic registration and analysis.

The lower strip of Fig. 2 illustrates how the use of magnetic tape as an intermediate recording modality can provide a compromise between the dynamic limitations of direct writers and the desire for increased accuracy in oscillographic registration. In essence, cardiovascular sounds can be recorded as frequency modulated signals at high tape speed and played back into the direct writer at a lower speed. This maneuver serves the dual purpose of effectively multiplying the phonocardiographic paper speed by the ratio of the higher to the lower tape speed, and of extending the response capacity of the direct writer by essentially the same ratio. The advantages

*Elema-Schonander Mingograph Recorder (distributed in the United States by Schick X-Ray Company, Inc., Chicago, Ill.); The Schwarzer Co., Boston, Mass.

of the scheme are offset to some extent by the loss of the desired immediacy of registration but this disadvantage would probably not be very important when dealing with special investigative and clinical problems. In addition to the achievement of better phonocardiograms by means of a nonphotographic intermediate process, some possibility also exists for further significant improvement in the quality of direct writers per se.

The testing procedures described in this paper and its companion[5] have led us to the optimistic conclusion that direct writing phonocardiography will eventually occupy much the same type of role in biomedical instrumentation that the direct writing electrocardiograph has come to assume. By this we mean that an instrument similar to that which was employed in this study will quickly and conveniently provide adequate clinical information in most instances but that the use of more elaborate and time-consuming procedures will still be advisable for investigative and clinical problems of a more demanding nature.

Summary

Despite the inherently limited response capability of mechanical recorders we have found it possible to develop a direct writing phonocardiograph which produces tracings that compare rather favorably with optical galvanometric registration. Phonocardiograms recorded simultaneously by the two methods from 30 subjects with auscultatory abnormalities showed very little loss of diagnostically important information (important at least, by present standards) by the direct writer. The use of the direct writing technique eliminates the effort and delay of photographic processing and the immediacy of the results affords a means for continuously monitoring the records for quality and special content at the time of registration.

Our experiences with the instrument described in this report indicate that properly designed direct writing phonocardiographs may be used to real advantage in routine clinical applications.

REFERENCES

1. Brody, D. A.: The prospects for direct-writing phonocardiography, with a short critique of spectrophonocardiography, Am. Heart J. 59:90, 1960.
2. Groom, D., Sihvonen, Y. T., and Sprouse, J. H.: A high sensitivity pickup for cardiovascular sounds, Am. Heart J. 54:592, 1957.
3. Lawson, J. D.: A simplified method of recording heart sounds, New England J. Med. 261:1235, 1959.
4. Caniggia, A.: Fonocardiografia, Cardiologia practica 7:27, 1955.
5. Erb, B. D., Evans, J. W., and Brody, D. A.: Application of direct-writing phonocardiography to clinical diagnosis and training. (In preparation.)
6. Gallavardin, L.: Cited by McKusick, V. A.: Cardiovascular sound in health and disease, Baltimore, 1958, The Williams & Wilkins Company, pp. 176 and 267.

Left ventricular parietal block produced by transventricular aortic commissurotomy

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Left axis deviation, or leftward deviation of the mean QRS forces in the frontal plane of the conventional electrocardiogram to more than minus 30 degrees has been interpreted as evidence of a conduction defect in the parietal branches of the left bundle of His.[1,2] The duration of the QRS interval need not be prolonged. The angle between the initial and terminal 0.04-second QRS forces remains less than 45 degrees in patients with *diffuse* fibrosis of the free wall of the left ventricle associated with either coronary disease or myocardial hypertrophy. This angle is widened, however, in some patients with *localized* myocardial infarction. In 1950 First and associates[3] described peri-infarction block, characterized by prolonged duration of QRS complexes together with an abnormal initial QRS vector, i.e., Q wave, typical of myocardial infarction and leftward rotation of the terminal forces of ventricular depolarization. Grant[1,2] subsequently emphasized the frequent association of left axis deviation with this infarction pattern. Although the angle between the initial and terminal QRS forces was characteristically widened to more than 100 degrees, usually there was no prolongation of the duration of the QRS interval in almost one half of the cases of anterolateral myocardial infarction.

Recognition of left axis deviation of the mean QRS vector due to marked leftward rotation of only the terminal forces of ventricular depolarization after transventricular aortic commissurotomy led to a survey of preoperative and postoperative electrocardiograms in a number of patients subjected to this procedure. Since very few of these surgical cases presented even transient electrocardiographic evidence of significant changes in initial QRS forces suggesting myocardial infarction, the demonstration of usually persistent changes in terminal forces resulting from aortic commissurotomy reveals another mechanism for the production of such parietal conduction defects.

Materials and methods

Preoperative and postoperative electrocardiograms were available for 29 patients in whom aortic commissurotomy had been performed by Dr. K. Alvin Merendino by the "closed" method utilizing a transventricular approach with a small modified Bailey dilator introduced into the left ventricle through a stab wound near the apex and passed blindly toward the aortic valve.[4] Two patients who initially had typical anterolateral peri-infarction block, and another who had left axis deviation with a narrow initial terminal QRS angle

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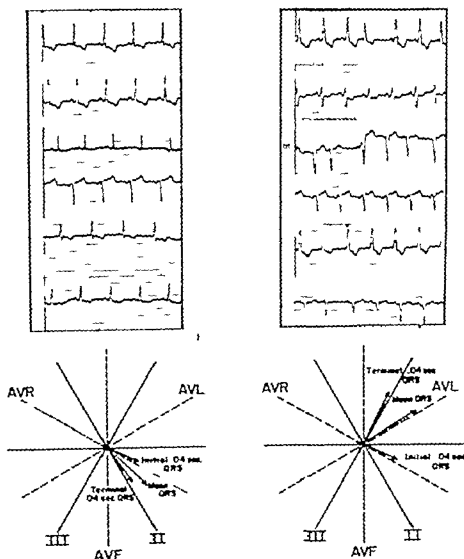


Fig. 1. Changes in the frontal plane projection of the electrocardiogram in a representative patient with aortic stenosis after transventricular aortic commissurotomy.

preoperatively were eliminated from this study. The first postoperative tracing was obtained within 1 day after operation in 11 patients, from 2 to 10 days postoperatively in 9, from 11 to 20 days in 3, and at 2, 6, and 8½ months after operation in 3 patients. Continuous electrocardiographic monitoring throughout the operation was carried out in 3 patients.

For comparative purposes, preoperative and postoperative tracings of two additional groups of patients were reviewed also. (1) In 25 patients who underwent left atriotomy for mitral commissurotomy, initial postoperative tracings were obtained within 1 day in 12, from 2 to 10 days in 11, and from 11 to 14 days in the other 2 patients. (2) In 15 patients who were subjected to a right ventriculotomy during cardiopulmonary bypass for repair of interventricular septal defect (10 patients), isolated pulmonic stenosis (2 patients), combined interventricular septal defect and pulmonic stenosis (2 patients), or ruptured sinus of Valsalva (1 patient), initial postoperative tracings were obtained within 1 day in 7 and from 2 to 7 days postoperatively in the other 8 patients.

All preoperative electrocardiograms were standard 12 lead tracings. In a few postoperative records not all precordial leads were obtained because of technical limi-

tations imposed by the surgical dressing on the chest. Mean initial 0.04-second and terminal 0.04-second QRS vectors were plotted by the method described by Grant.[7] These vectors were recorded to the nearest 5 degrees. In addition the angles between the initial and terminal 0.04-second QRS vectors as well as changes in QRS duration after operation were determined.

Results

Left ventriculotomy. The 26 control tracings which were recorded prior to ventriculotomy showed a normally directed mean QRS vector and an angle of less than 90 degrees between the initial and terminal 0.04-second QRS vectors (Table I). Postoperatively 15 of the 26 patients showed a definite superior or leftward shift of the terminal forces of ventricular depolarization (Fig. 1). A significant initial vector deformity that was suggestive of myocardial infarction occurred in only 2 cases: one patient actually developed a left bundle branch block transiently, and another had initial vector changes of anterolateral myocardial infarction permanently.

All but 2 patients showed left axis deviation in the first tracing postoperatively in addition to the shift of the terminal depolarization forces. Another patient demonstrated left axis deviation in a subsequent tracing recorded 5 months after operation. Five patients showed left axis deviation only temporarily or intermittently, and only 1 patient exhibited later a return to the preoperative direction of the terminal forces of ventricular depolarization.

Significant prolongation of the QRS interval to 0.12 second or longer was observed in only 4 patients postoperatively.

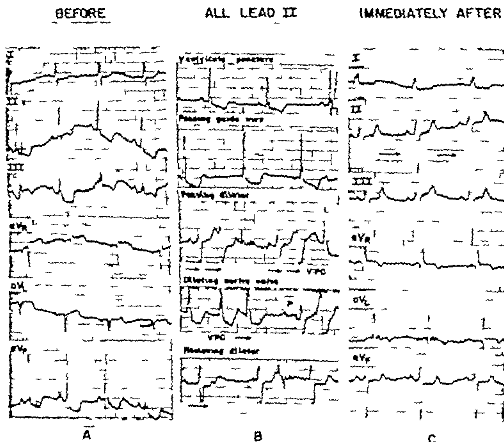


Fig. 2. Tracings obtained during operation (chest open). A, Before introduction of aortic dilator. B, Lead II recorded during passage of dilator. Note development of left axis deviation after marked arrhythmia during manipulation of instrument. C, Immediately after withdrawal of dilator.

Three patients were monitored electrocardiographically throughout the operation. Ventricular depolarization prior to the introduction of the valvulotome into the left ventricle was normal in each. All suddenly developed marked terminal but not initial changes in ventricular depolarization, as well as left axis deviation of the mean QRS vector at the time the valvulotome was passed toward the aortic valve (Fig. 2). Again, in all 3 patients the duration of QRS forces was prolonged suddenly, yet in no instance did this persist beyond the first postoperative day. Left axis deviation of the mean QRS vector was observed temporarily in 2 patients (for only 20 minutes in one, and intermittently for 6 days in the other), whereas the terminal depolarization forces remained abnormal in all 3 during the period of postoperative observation (2, 7, and 10 days).

Careful review of the operative and postoperative records provided no evidence that the electrocardiographic changes were related to surgical complications such as loss of blood, anoxia, or hypotension.

Left atriotomy. In 16 patients the electrocardiograms before operation showed an entirely normal ventricular activation, whereas in 9 others the electrocardiograms demonstrated right axis deviation of the mean QRS vector. Operation did not change these patterns.

Right ventriculotomy. In 4 patients the electrocardiogram showed normal ventricular activation before operation, but postoperatively it showed right axis deviation in one patient, and right bundle branch block in another.

Tracings from 8 patients preoperatively showed right axis deviation, as well as anteriorly directed initial and terminal

Table I

Patient	Preoperative QRS forces: Mean	Initial 0.04 sec.	Terminal 0.04 sec.	Angle between	Time after operation for first ECG	Post opera-: Mean
	(degrees)					
B.	60	75	30	45	Hours	−30
W	30	55	0	55	6 mo.	15
J	30	60	30	30	3 days	−20
H	0	5	−5	10	9 days	15
C	5	35	0	35	Hours	5
F	40	50	15	35	Hours	−40
R	60	65	55	10	3 days	30
R	35	60	−10	70	Hours	−30
O D	60	70	−5	75	1 day	50
P	50	20	40	20	3 days	−45
O'K	65	55	70	15	2 day	−40
McS	40	60	30	30	8 day	20
McD	40	60	0	60	20 day	−15
P	55	70	30	40	11 days	−25
S	0	30	−40	70	18 days	−60
C	5	40	−50	90	4 day	−55
McC	20	60	0	60	Hours	5
O'F	15	30	−50	80	3 days	15
C	0	35	−30	65	Hours	60
[illegible]	10	−10	5	15	1 day	0
B	−10	0	−30	30	1 day	−10
L.W	60	60	30	30	2 mo.	−30
K.	30	35	0	35	Hours	−10
McF	15	0	30	30	Hours	−60
T.L.	10	20	0	20	Hours	−45
M D	−10	15	−25	40	Hours	−50

0 04-second QRS vectors which were suggestive of right ventricular hypertrophy After operation 3 tracings showed right bundle branch block and 1 returned to normal.

Two patients showed right ventricular hypertrophy without right axis deviation before operation and one developed right axis deviation after operation

Another patient had a left bundle branch block both before and after the operation

Discussion

Except for the occasional instance of marked emphysema, deviation of the mean QRS forces to more than minus 30 degrees, or above the lead axis of aV_L in the frontal plane, represents a conduction defect Indeed Grant[1,4] has postulated a block in the superior division of the left bundle system Whereas anatomic division into superior and inferior fibers has been demonstrated in the human heart,[5] specific interruption of any of these fibers in left ventricular parietal block has not been established. It is of interest therefore that leftward deviation of the mean and terminal 0 04-second QRS forces is observed during transventricular aortic commissurotomy Since significant changes in initial 0 04-second QRS forces were absent in all but 2 of the 15 patients sufficient myocardial injury and necrosis to manifest myocardial infarction was usually lacking Furthermore, the changes observed suggested damage only to the fibers of the left bundle When electrocardiograms were carefully monitored in 3 patients passage of the dilator through the free wall of the left ventricle did not produce these changes but further passage up the outflow tract of the ventricle

the QRS forces			*Changes in QRS forces after operation*				
Initial 0.04 sec.	*Terminal 0.04 sec.*	*Angle between*	*Mean QRS*	*Initial QRS*	*Terminal QRS*	*Angle*	*QRS duration (sec)*
(degrees)			*(degrees)*				
20	−55	75	−90	55	85	+30	+ 05
40	5	25	−15	−25	+5	−30	0
65	−45	110	−50	+5	75	+80	0
25	0	25	+15	+20	+5	+15	0
10	−10	20	0	25	10	−15	0
25	−70	95	−80	25	−85	+60	+ 03
30	10	25	−30	−30	−45	+15	− 01
60	−45	105	−65	0	−35	+35	0
60	35	25	−10	−10	+40	−50	0
0	−75	75	−75	−20	−115	+55	0
65	−60	105	−105	+10	−130	+90	+ 03
35	0	35	−20	−35	−30	−5	0
60	−60	120	−55	0	−60	+60	+ 01
70	−60	130	−80	0	−90	+90	+ 02
60	−75	135	−60	+30	−35	+65	+ 02
50	−80	150	−80	0	−90	+90	+ 02
60	0	60	−15	0	0	0	0
0	−45	45	0	−30	+5	−35	+ 01
35	75	40	+60	0	105	−25	0
−30	10	40	−10	−20	+5	+25	0
5	−20	25	0	+5	+10	−5	0
60	−60	120	−90	0	−90	+90	0
60	−50	110	−40	+5	50	+55	0
45	−65	110	−75	+45	95	+80	+ 04
45	−60	105	−55	+25	−60	+85	0
15	−70	85	−40	0	−45	+45	0

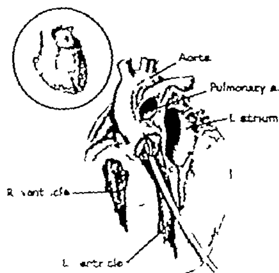


Fig. 3. Schematic representation of passage of aortic dilator through left ventricular cavity, showing its proximity to the superior division of the left conducting bundle.

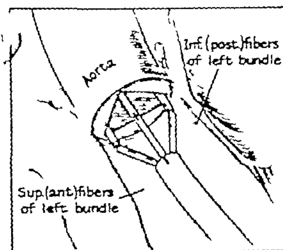


Fig. 4. Schematic representation of proximity of valvulotome to superior or anterior fibers of the left bundle.

promptly initiated the left axis deviation (Fig. 2). It can be assumed that either the superior group of fibers of the left bundle which extends to the superior aspect of the left ventricle was "damaged" or the direction of spread of the excitation was upward from the diaphragmatic region of the left ventricle so that the QRS forces pointed superiorly and leftward. Grant's impressions that damage to the superior division may be responsible for left axis deviation is also supported by recent experimental work. Disruption of the superior fibers in the dog heart (which are easily visualized subendocardially) rotates the terminal QRS vector more superiorly.[3] The sudden onset of these changes in depolarization while the valvulotome is passed along the outflow tract of the left ventricle strongly favors direct local damage to the fibers. Furthermore during passage of the instrument from the apex of the left ventricle to the aortic valve in postmortem specimens the dilator impinges on the left ventricular septal surface in the area of these conducting fibers (Figs. 3 and 4). Since the conduction defect is only transient in some patients the damage to the fibers may be limited to edema and or hemorrhage.

Summary

Preoperative and postoperative electrocardiograms of 29 patients who underwent transventricular aortic commissurotomy were reviewed. Fifteen of 26 tracings which showed normal ventricular depolarization forces preoperatively showed left axis deviation with significant changes in direction of the terminal depolarization forces postoperatively. In 3 patients in whom the electrocardiogram was monitored during operation these changes were observed as soon as the aortic dilator was advanced toward the aortic valve. The tracings taken in a comparable number of patients who were subjected to right ventriculotomy or left atriotomy failed to show similar changes.

The acute occurrence of this conduction defect in the apparent absence of myocardial infarction is attributed to the mechanical trauma to the fibers of the superior division of the left bundle caused by the dilator as it is passed through the outflow tract of the left ventricle.

REFERENCES

1. Grant, R. P.: Left axis deviation, Circulation 14:233, 1956.
2. Grant, R. P.: Left axis deviation, Mod. Concepts Cardiovas. Dis. 27:437, 1958.
3. First, S. R., Bayley, R. H., and Bedford, D. R.: Peri-infarction block; electrocardiographic abnormality occasionally resembling bundle branch block and local ventricular block of other types, Circulation 2:31, 1950.
4. Grant, R. P., and Murray, R. H.: The QRS

complex deformity of myocardial infarction in the human subject, Am J Med. 17:587 1954.
5 Grant, R. P., and Dodge H T: Mechanisms of QRS complex prolongation in man. Left ventricular conduction disturbances, Am J Med. 20:834, 1956.
6 Logan, G. A., Merendino, K. A., Bergy G. G., and Bruce, R. A A preliminary evaluation of transventricular aortic commissurotomy with an improved dilator New England J Med. 255:802, 1956
7 Grant, R. P Clinical electrocardiography The spatial vector approach, New York, 1957 McGraw Hill Book Company Inc
8. Widran, J., and Lev M The dissection of the atrioventricular node, bundle and bundle branches in the human heart, Circulation 4:863 1951
9 Samson, W. E., and Scher A. M Unpublished data, 1960.

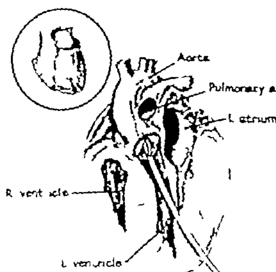


Fig. 3. Schematic representation of passage of aortic dilator through left ventricular ca ity showing its proximity to the superior division of the left conducting bundle.

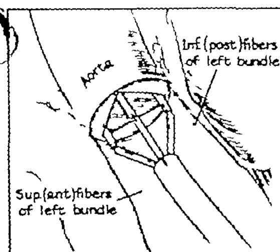


Fig. 4. Schematic representation of proximity of valvulotome to superior or anterior fibers of the left bundle.

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REFERENCES

1. Grant, R. P.: Left axis deviation, Circulation 14:233, 1956.
2. Grant, R. P.: Left axis deviation, Mod. Concepts Cardiovas. Dis. 27:437, 1958.
3. First, S. R., Bayley, R. H., and Bedford, D. R.: Peri-infarction block: electrocardiographic abnormality occasionally resembling bundle branch block and local ventricular block of other types, Circulation 2:31, 1950.
4. Grant, R. P., and Murray, R. H.: The QRS

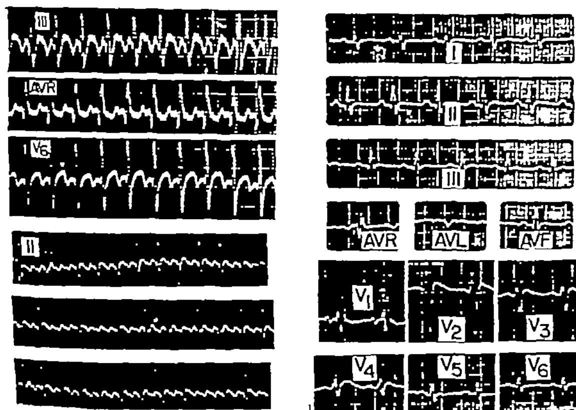


Fig. 1 The electrocardiogram taken on admission (*top 3 strips on the left*) showed atrial flutter with a 2:1 A-V block and ventricular rate of over 200 beats per minute. After partial digitalization (*bottom 3 strips on the left all of Lead II*) the degree of block increased but was variable, and the atrial flutter is more obvious. After complete digitalization (*right half of the illustration*) a sinus rhythm was established at a rate of approximately 130 beats per minute. A right bundle branch block is present.

normal. Sections of the left ventricle and interventricular septum demonstrated a number of gelatinous, firm gray areas (Fig. 2). Both ventricles were of normal thickness. There were ecchymoses in the epicardium of the right atrium, particularly the sulcus terminalis and the anteromedial surface (Fig. 3). Similar ecchymoses of the right atrium were present in Case 1 of the study by Berman. The lumina of the main coronary arteries were patent, and the walls were thin and pliable. The right coronary artery crossed the crux of the heart and supplied the A-V node. The sinus node artery arose from the left circumflex ramus.

According to the routine procedure for the study of the conduction system in this laboratory,[25,26] sections were made at intervals of 2 mm. On microscopic examination the sinus node artery was involved by a granular and cystic degeneration of the media and a variable amount of endothelial proliferation. In several areas there were hemorrhages in the tunica media (Figs. 4, 5, and 8,A). The involvement was intermittent, with some segments of the artery almost normal; the lumen was patent in all sections. The branches were less involved than the main sinus node ... sinus node fibers were degenerative ... this degeneration did not always ...

points of arteriopathy, most of the sinus node fibers appeared to be normal. In one area there was hemorrhage into the node.

Histologically, the bundle of His and the main bundle branches were normal, but the underlying myocardium of the interventricular septum was fibrotic. Scattered myocardial fibers in these regions were degenerated. The anterior half of the A-V node and its artery were normal. In the posterior half the artery to the A-V node was almost occluded by an endothelial proliferation which was Schiff positive (Fig. 7). Since the blood supply to the A-V node was from its posterior margin, as it normally is,[25,26] the encroachment on the lumen compromised the blood supply to the node. Several branches of the artery of the main A-V node exhibited mural degeneration and hemorrhage similar to that which involved the artery of the sinus node; some of the hemorrhage extended into the A-V node (Fig. 7).

Small arteries throughout the myocardium occasionally showed mural degeneration, but not so frequently as in the pacemaker and the A-V node. None of the arteriopathy had perivascular cellular reaction. No arteriopathy could be related to the areas of ventricular fibrosis. On careful searching similar arteriopathy was found in the lung in tissue (Fig. 8,B and C) ... rarely ...



Fig. 2. Two transverse slices of the left ventricle. Coalescent areas of fibrosis are apparent, particularly near the epicardium.

muscle, but this finding was not frequent or extensive except in the heart. The extracardiac arteriopathy would not be considered significant except that it was of the same type as that found in the cardiac nodes. Selected sections of the aorta and main pulmonary artery were normal. The main coronary arteries were normal in most sections, but a few points there was early medial degeneration the type seen in the arteries to the nodes (Fig. 1D).

Discussion

Two features of this case which merit particular attention are the arteriopathy of the cardiac nodes and the degeneration of the fibers of the nodes. The clinical significance of these two features is indicated by the occurrence of disturbances in cardiac rhythm and conduction during life.

Dysfunction of the sinus node and the A-V node was probably the result of two parallel pathologic conditions. One involved the fibers of the sinus node directly, whereas the other produced an arteriopathy which compromised the arterial supply to the A-V node. It is doubtful that focal ischemia contributed to dysfunction of the sinus node, but the nature of the arteriopathy appeared to be the same in both cardiac nodes. Unrelated to the degeneration of the arteries in the sinus node there were a few degenerating fibers which resembled those seen in myocardium of the ventricles and in skeletal muscle. In the A-V node there was no apparent degeneration of the fibers of the node, but the lumen of the nutrient artery was compromised. In addition, some of the major branches of this artery were incompletely ruptured, with hemorrhage into the A-V node.

The pathogenesis of the atrial flutter and heart block is probably related to the morphologic changes. Degeneration of fibers in the sinus node plus small areas of focal hemorrhage may have contributed to suppression of normal sinus pacemaking. This, coupled with irritable areas of extranodal atrial myocardium, may have led to atrial flutter.[17,18] The sinus node was still capable of resuming command of the heart, however, since sinus rhythm was restored and persisted until death.

Heart block was a terminal feature, at which time the sinus node was apparently still firing but evoking no ventricular response. Hemorrhage into the A-V node may have contributed to this but did not seem to be extensive enough to have disrupted conduction. A more likely explanation is severe focal ischemia caused by failure of perfusion through the narrowed artery of the A-V node. If a transient block of the A-V node occurred initially, the fibrotic left ventricle could not respond with a normal increase in stroke output to compensate for a bradycardia accompanying heart block. With diminution in cardiac



Fig. 3. A photograph of the anteromedial surface of the right atrium which has been cut from the heart along the atrioventricular sulcus and interatrial septum. The arrow indicates the ecchymoses, which were also present in the sulcus terminalis (not shown). SVC, Superior vena cava; AP, Right atrial appendage.



Fig. 4. Photomicrographs of the wall of the sinus node artery. The extensive hemorrhagic degeneration of the tunica media is seen in *A* (Goldner trichrome stain, ×64). *B* is an elastic stain of the same section showing that the degenerative process lies between the internal and external elastic laminae (Verhoeff-van Gieson stain, ×64). *C* is higher magnification of edial hemorrhage and degeneration in one segment of the arte (Goldner trichrome stain, ×160)



Fig. 5. Two photomicrographs illustrating the relationship of the nuclei of the smooth muscle of the tunica media to the cysts. A is of the sinus node artery 6 mm. upstream from the section in Fig. 4. Note how the smooth muscle nuclei seem elongated and hug the cyst (Goldner trichrome stain, ×160). B is a section of the A-V node artery showing the similar relationship of the nuclei to the cyst (periodic acid-Schiff stain, ×319).

output perfusion through the narrowed artery of the A-V node failed quickly.

It is assumed that the degeneration of fibers of the sinus node is similar in etiology to degeneration of fibers of other myocardium and skeletal muscle, but the tunica media of the artery is composed of smooth muscle. Degeneration of smooth muscle has been described in progressive muscular dystrophy,[illegible] but there has also been authoritative denial of its existence.[illegible] The reason for this difference in observations is not clear. Possibly the size of the arteries which are usually examined accounts for its escaping attention, for the predominant involvement in the present case was of arteries which were 1 mm. or less in diameter. Other authors have called attention to the likelihood of involvement of the small vessels in muscular dystrophy because of the occurrence of acrocyanosis[13] and other vasomotor phenomena.[14] It is possible, of course, that some patients with progressive muscular dystrophy have arteriopathy and involvement of extravascular smooth muscle, whereas other patients do not.

None of the arteries which were involved

had a surrounding inflammatory reaction which differentiates the process from the various arteritides. The arteriopathy was a noninflammatory degeneration in most areas cystic and granular but sometimes associated with mural hemorrhage. It resembled the pathologic condition of larger vessels (aorta and main pulmonary artery) in Marfan's syndrome but in the present case the large vessels were spared. A similar degenerative arteriopathy has been observed in three patients with so-called primary pulmonary hypertension another disease in which sudden death is a common clinical feature.[11,41] As an additional feature in common both muscular dystrophy[19] and primary pulmonary hypertension[21] are adversely affected by pregnancy.

There are other features which are common to both muscular dystrophy and Marfan's syndrome. In both diseases the victims frequently die suddenly. In both diseases there are ocular abnormalities. Although ectopia lentis is the hallmark of ocular involvement in Marfan's syndrome a number of other ocular abnormalities occur[22] whereas in muscular dystrophy (it is generally believed that both progres-

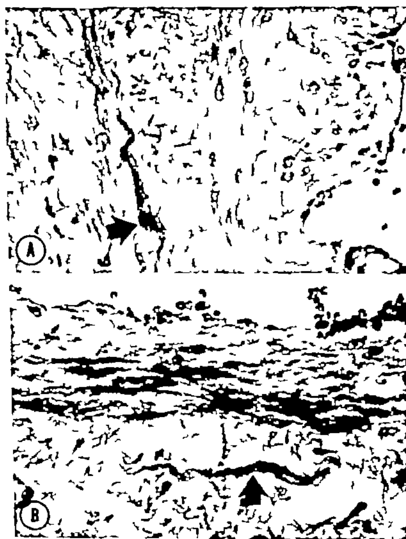


Fig. 6. Photomicrographs of sections of the sinus node taken 10 mm. apart. In each the arrow indicates a degenerating sinus node fiber adjacent to the sinus node artery. In *A* the artery shows both cystic degeneration and endothelial proliferation, whereas the changes in the artery in *B* are minimal (Goldner trichrome stain ×160).



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sive and nonprogressive muscular dystrophy are merely different forms of one large pathologic entity[1,20]) premature formation of cataracts, pupillary dysfunction and congenital deformity of the eyelids have been described[14] The familial incidence of both diseases is well known. Finally both diseases are associated with musculoskeletal deformities. In Marfan's syndrome the muscular degeneration has been explained on the basis of primary skeletal lesions especially those producing instability of the joints,[28] whereas in progressive muscular dystrophy the scoliosis and deformities of the chest wall have been explained as secondary to the disease.[1,21]

Perhaps the skeletal deformities in progressive muscular dystrophy are an associated primary process rather than secondary to the muscle weakness. In discussing the occasional incorrect diagnosis of Marfan's syndrome as progressive muscular dystrophy and vice versa, McKusick[28] concludes that the two diseases are unrelated. However if future examination of the small arteries from the heart of patients with progressive muscular dystrophy (or Marfan's syndrome) confirms that the histopathology is similar to that of larger vessels in Marfan's syndrome the question of an interrelationship of the two diseases should be re-examined

Summary

The case of a young man with progressive muscular dystrophy who had both cardiac arrhythmias and heart block is described At necropsy degeneration of fibers in the sinus node was found and an unusual noninflammatory degeneration of the arteries which supply both the sinus node and the atrioventricular node. Similar involvement was observed in other arteries,



Fig 8 Four examples of the arteriopathy in this case, illustrating its general similarity *A* is a section of the sinus node artery 8 mm. downstream from the section in Fig 4 here showing endothelial proliferation similar to that in the major artery of the A V node, though less extensive (Verhoeff van Gieson stain, ×64). A similar but more modest involvement of an artery in the muscularis of the large intestine is shown in *B* (Verhoeff-van Gieson stain, ×64). Similar invol ement of an artery in the lung is shown in *C* (Goldner trichrome stain, ×64). The wall of the left anterior descending c[illegible] pro-liferation is shown in *D* (Goldner trichrom

but much less frequently than in the cardiac nodes. The pathogenesis of the arrhythmias and heart block which are commonly seen in progressive muscular dystrophy is discussed in the light of these observations.

REFERENCES

1. Adams, R. D., Denny-Brown, D., and Pearson, C. M.: Diseases of muscle: study in pathology, New York, 1953, Paul B. Hoeber, Inc.
2. Ask-Upmark, E.: Cardiovascular observations in myasthenia gravis and dystrophia myotonica, Acta med. scandinav. 116:502, 1944.
3. Berenbaum, A. A., and Horowitz, W.: Heart involvement in progressive muscular dystrophy: report of a case with sudden death, Am. Heart J. 51:622, 1956.
4. Bevans, M.: Changes in the musculature of the gastrointestinal tract and in the myocardium in progressive muscular dystrophy, Arch. Path. 40:225, 1945.
5. Boas, E. P., and Lowenburg, H.: The heart rate in progressive muscular dystrophy: studies with the cardiotachometer, Arch. Int. Med. 47:376, 1931.
6. Cabot Case #33311, New England J. Med. 237:163, 1947.
7. Cohen, S.: Myocardial fibrosis in progressive muscular dystrophy, J. Med. 17:26, 1936.
8. DeWind, L. T., and Jones, R. J.: Cardiovascular observations in dystrophia myotonica, J.A.M.A. 144:299, 1950.
9. Evans, W.: The heart in myotonia atrophica, Brit. Heart J. 6:41, 1944.
10. Fisch, C.: The heart in dystrophia myotonica, Am. Heart J. 41:525, 1951.
11. Gailani, S., Danowski, T. S., and Fisher, D. S.: Muscular dystrophy: catheterization studies indicating latent congestive heart failure, Circulation 17:583, 1958.
12. Globus, J. H.: The pathologic findings in the heart muscle in progressive muscular dystrophy, Arch. Neurol. & Psychiat. 9:59, 1923.
13. Goodhart, S. P.: Progressive muscular dystrophies: necropsy studies in four cases, J. Mt. Sinai Hosp. 9:514, 1942.
14. Grandell, F.: The heart in progressive muscular dystrophy, Am. J. M. Sc. 231:659, 1956.
15. Jackson, A., and O'Donnell, M. J.: Progressive muscular dystrophy with A-V atrial flutter, Am. Heart J. 59:277, 1960.
16. Kilburn, K. H., Eagan, J. T., Sieker, H. O., and Heyman, A.: Cardiopulmonary insufficiency in myotonic and progressive muscular dystrophy, New England J. Med. 261:1089, 1959.
17. Leiter, L.: Metabolic heart diseases, Mod. Concepts Cardiovas. Dis. 26:401, 1957.
18. Maas, O., and Paterson, A. S.: Dystrophia myotonica as a generalized disease, Monatschr. Psychiat. u. Neurol. 113:79, 1947.
19. Nothacker, W. G., and Netsky, M. G.: Myocardial lesions in progressive muscular dystrophy, Arch. Path. 50:578, 1950.
20. Rubin, I. L., and Buchberg, A. S.: The heart in progressive muscular dystrophy, Am. Heart J. 43:161, 1952.
21. Weisenfeld, S., and Messinger, W. J.: Cardiac involvement in progressive muscular dystrophy, Am. Heart J. 43:170, 1952.
22. Zatuchni, J., Aegerter, E. E., Molthan, L., and Shuman, C. R.: The heart in progressive muscular dystrophy, Circulation 3:846, 1951.
23. James, T. N.: Anatomy of the human sinus node, Anat. Rec. (In press.)
24. James, T. N.: Morphology of the human atrioventricular node with remarks pertinent to its electrophysiology, Am. Heart J. 62:756, 1961.
25. James, T. N., and Burch, G. E.: The atrial coronary arteries in man, Circulation 17:90, 1958.
26. James, T. N.: Anatomy of the coronary arteries, New York, 1961, Paul B. Hoeber, Inc.
27. James, T. N.: Myocardial infarction and atrial arrhythmias, Circulation. (In press.)
28. James, T. N., and Hershey, E. A.: Experimental studies on the pathogenesis of atrial arrhythmias in myocardial infarction. (Unpublished observations.)
29. Rohrer, K.: Cited by Maas and Paterson.
30. James, T. N.: On the cause of syncope and sudden death in primary pulmonary hypertension, Ann. Int. Med. (In press.)
31. James, T. N.: Degenerative arteriopathy with pulmonary hypertension: a revised concept of so-called primary pulmonary hypertension, Henry Ford Hosp. Med. Bull. 9:271, 1961.
32. McKusick, V. A.: Heritable disorders of connective tissue, ed. 2, St. Louis, 1960, The C. V. Mosby Company.
33. Milhorat, A. T.: Observations on the pathogenesis of progressive muscular dystrophy, Proc. First and Second Medical Conferences, New York City, 1951 and 1952, Muscular Dystrophy Association of America, Inc., pp. 78-83.

A form of vascular disease relatively frequent in the Orient

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During a recent visit† to six university medical centers in Japan and to five centers in Korea, I had the opportunity to examine 3 currently hospitalized patients with Takayasu's disease, otherwise known as pulseless disease[1] or the "young female arteritis" type of aortic arch syndrome.[2] The clinical, histopathologic, and radiographic data in 9 other cases were reviewed in detail. Furthermore, Dr. Keiji Sano of Tokyo University reviewed with me various aspects in the series of 42 cases which he and Professor Kentaro Shimizu have investigated. Having discovered only one definite and two possible instances of this particular form of aortic arch syndrome in my personal experience in the United States,[3,4] despite constantly watching for the disorder since 1950, I can say confidently that the disease is much more frequent in the Orient. The relatively frequent reports of this condition from both Japan[5-7] and Korea[12,13,14] and from elsewhere in the Orient[11,20,24,25,40] would suggest that such is the case. Several clinical and pathologic features not previously known to me were emphasized by the recent experience and are outlined here. In addition, a progress report is provided on 2 patients who were first seen 12 and 10 years ago, and another recently studied patient is described.

Vasography. In 1908, before the Twelfth Congress of the Japanese Ophthalmologic Society, Takayasu, an ophthalmologist then in Tokyo, reported a case of strange changes in the central retinal vessels.[11] The ocular changes in Takayasu's patient, a 21-year-old woman whose symptoms had begun some years previously, consisted of cataract and a wreath of interanastomosed arteries and veins surrounding the optic disc. The published abstract (in Japanese) occupied only about one page and concluded with the author's stating, "I do not know the exact nature of this disease." However, in the discussion that followed, Professor Onishi of Kyushu University stated that he had encountered these ocular changes in a patient who had no pulses in the upper part of the body.

Thereafter, scattered cases were reported, mainly by ophthalmologists.[18] In the nineteen-thirties, Dr. Sato of Tokyo University explored the neck of a patient and concluded that the main arterial trunks were occluded at the aortic arch.[8] The first autopsy of a case in Japan is said to be that reported by Oota,[9] in 1940

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†I am indebted to Professor Hideo Ueda, Tokyo University, and to his associates Dr. Masahiro Ito and Dr. Kenji Ueda for assistance in planning these visits. Dr. S. K. Suh provided similar assistance in Korea. The institutions visited were (in Japan) Tokyo University, Tokyo Medical and Dental University, Juntendo University (Tokyo), Kyoto University, Osaka University, and Nagoya University; (in Korea) Severance Hospital, Seoul National University Hospital, Soo Do Medical College Hospital, National Medical Center (Seoul), and Presbyterian Medical Center (Chonju).

However at least four autopsies had been done elsewhere by Savory[22] in England (1856), Beneke[1] in Germany (1925), Harbitz,[12] in Norway (1926) and Marinesco and Kreindler[40] in Romania (1936). In 1952 Caccamise and Williams[8] were able to find reports of 52 cases in the Japanese literature—almost certainly a minimal figure. The condition came to be known in Japan as Takayasu's disease or pulseless disease.[3]

Much less frequently cases were reported in the West; for example, Kussmaul[14] described a case in Germany in 1872 and a patient was separately reported on by Harbitz[12] and Raeder[34] of Norway in the nineteen twenties. In 1944, Martorell and Fabré[30] of Barcelona described a case under the title of "the syndrome of obliteration of the supra-aortic trunks." With the irrationality characteristic of eponymization the disorder is sometimes referred to as Martorell's syndrome. In reporting a case in 1946 Frøvig of Oslo first suggested the designation *aortic arch syndrome*.[11] In 1953 Ross and McKusick[2] reviewed the aortic arch syndrome in a general way and suggested *young female arteritis type of aortic arch syndrome* as a designation for the variety under discussion here. Ask Upmark[17,19,20] has observed several cases in Sweden. In 1936 Marinesco and Kreindler[40] observed a typical case in Bucharest, Romania. From Paris, Maspetiol and Taptas[33] reported a case in 1948. Cases were reported in Britain by Sir Thomas Lewis with Stokes, in 1942[36] and by Skipper and Flint[44] in 1952. The first British case was that of Savory[22] who in 1856 described a 22 year-old woman in whom the main arteries of both upper extremities and of the left side of the neck were throughout completely occluded.

The first American report I have found is that of Elliot, Usher and Stone[41] of Santa Barbara, California, who at the American Heart Association meeting of 1938 described a 26-year-old Mexican laborer who had the onset of syncopal attacks and was found to have no pulses in the arms and neck, hypertension in the legs, tachycardia, and a loud continuous bruit about the clavicles. (That the patient was male does not mean that he did not suffer from the "young female arteritis" type of aortic arch syndrome. See Table I.) He developed bilateral cataracts and hemiplegia during the 16 months of observation. The authors suggested that a congenital anomaly of the vessels about the arch of the aorta was present—a mistaken impression of mine, too, when I saw my first instance of this disorder.[4]

Table I. Age of onset (Sano, 1961)

Age (yr.)	*Number of cases*
6–10	3
11–15	8
16–20	14
21–25	7
26–30	5
31–35	3
36–40	2
Total	42

40 females, 2 males

Clinical features. As is indicated in Table I, in a majority of the cases the age of the patient at onset of the condition is under 20 years, and almost all patients are female.

Giddiness and syncope are the most frequent symptoms; coldness, paresthesia, fatigue or other symptoms in the arm are the second most frequent symptoms, and changes in visual acuity are third.

The typical posture in about two thirds of the patients consists in holding the head inclined forward. It can be demonstrated that visual acuity in patients with pulseless disease is appreciably better on downward gaze than on horizontal or upward gaze.[7] In severe cases the hair is lost, the facial muscles atrophy, and the nasal septum is perforated.

In the eye, enophthalmos, atrophy of the iris and ciliary muscle, defective accommodation, cataract, and the striking retinal changes described by Takayasu are observed. Conjunctival hyperemia and dilated circumlimbal vessels, probably representing anastomoses between branches

A follow-up with autopsy was provided by Lande and Glynn,[41] who concluded that it could be considered "a classic case of Takayasu's disease with histological findings closely resembling syphilitic aortitis." They also wrote: "The Wassermann and Kahn reactions were repeatedly negative."

of the internal and external carotid arteries, are observed in some cases.

Various combinations of diminished or absent pulses in the branches of the aortic arch are observed. A murmur is likely to be audible over the vessels of the neck. In some cases the murmur may be continuous, suggesting patent ductus arteriosus by this character and by its location about the left clavicle.[5] Sir Thomas Lewis[30] was one of the first to write about this feature of the disease which suggested arteriovenous fistula. By ingenious experiments, Myers, Murdaugh, McIntosh and Blaisdell[37] provided an explanation for the continuous murmur of the aortic arch syndrome. They pointed out that a continuous murmur is likely to be present when the pressure beyond the obstruction or stenosis is appreciably lower than that proximal to the obstruction *throughout* the cardiac cycle. The murmur may be generated either in collaterals or at the site of stenosis.

Hypertension and tachycardia are usually present and are probably explicable on the basis of reduced pressure in the carotid sinuses. Furthermore, the carotid sinuses are abnormally sensitive and the attacks of syncope are in part carotid sinus syndrome.

Virtually all patients have a long-persisting elevation of erythrocyte sedimentation rate and many have mild leukocytosis. Some have had a positive serologic test for syphilis. That this is, at least in some instances, a "biologic false positive" should be investigated because of the youth and sex of the patients. Aortography is the definitive method for demonstrating the occlusion and stenosis of the aortic branches. The vertebral arteries are usually spared and vertebral arteriography is likely to demonstrate filling of the cerebral circulation even to the anterior fossa rather than the usual filling merely of the arterial tree in the posterior fossa.

Clinical features as found in 48 cases studied by Sano[44] are reviewed in Table II.

Histopathology. The histopathology is frequently that of a chronic arteritis, with round cells and giant cells involving all layers of the arterial wall. At other times the changes have been nonspecific, probably because the sections have been remote from the active process in time or anatomic site.

Features of particular interest. One of the patients I examined recently in Japan had aortic regurgitation. I find a description of aortic regurgitation in only two

Table II. Clinical features in 48 cases of pulseless disease (Sano, 1961)

Feature	*Number*	*Feature*	*Number*
Absent radial pulse	48	Perforated nasal septum	18
Increased sedimentation rate	48	Cerebral symptoms, including abnormal EEG	14
Sensitive carotid sinus	44	Cataract	14
Postural syncope	43	Reduced ocular pressure	13
Positive tuberculin test	41	Restricted visual fields	12
Hyperemia of bulbar conjunctiva	38	Cold skin	12
Characteristic posture	32	Atrophy of iris	9
Retinal vessel anastomoses	30	Speech defect	8
Tachycardia	30	Hyperopia	6
Interference with vision on looking up	29	Abnormal cardiac findings	5
Headache	28	Abnormal pulmonary findings	5
Absent distal common carotid pulse	29	Struma	5
Bruit in neck	25	Abnormal nail-bed capillaries	3 (out of 8 studied)
Elongated, dilated aortic arch with diminished pulsation	22 (out of 30 studied)	Memory disturbance	2
Photophobia	22	Superficial keratitis	2 (out of 23 studied)
Leukocytosis	21	Positive Wassermann test	2
Depressed ocular globe	21	Abnormal ECG	2
Loss of hair	20	Hemiplegia	[illegible]
Ocular pain	20		
Stiff shoulder			

cases reported in the literature.[17,41] Calcification of the descending thoracic aorta was also present in this patient, a 48-year-old woman.* The radial pulse had been absent for at least 15 years. Calcification is not a usual feature of the aorta in Takayasu's disease; however, calcification may occur if the patient survives sufficiently long. In one of the 10 cases reported by Birke, Fjrup and Olhagen[6] of Stockholm, calcification of the aorta was discovered as early as age 24 years and increased thereafter. In Patient E.L. (505915), a 33-year-old woman, we[7] observed the aortic arch syndrome and extensive calcification of the aorta, a feature which at the time we thought excluded Takayasu's disease.

A murmur over the abdominal aorta was present in 2 patients examined, and in one of these retrograde aortic catheterization from the femoral artery revealed a drop in pressure across a segment of the abdominal aorta. Although the predominant clinical manifestations of pulseless disease relate to the stenosis of the branches at the arch, the available autopsies[9,12] reveal that the underlying process is often a more general aortitis. Involvement of the descending thoracic and abdominal aorta with resulting "atypical coarctation"† occurs in a significant proportion of cases.

Atypical coarctation. Atypical coarctation is probably more frequent in Japan than is the usual typical coarctation of the aortic isthmus.[15] One large Tokyo University surgical service which performs much cardiovascular surgery had treated 10 cases of coarctation, 3 typical and 7 atypical.[15] Whereas the sex ratio of typical coarctation reflects the usual male preponderance, there is a considerable female preponderance among the cases of atypical coarctation. In many of the cases of atypical coarctation abnormality of the pulses at the arch are described. Cases of atypical coarctation due to aortitis in young persons are also relatively frequent in India.[47] It seems reasonable to suggest that much, perhaps most, of the atypical coarctation in the Orient is due to "young female arteritis." Such has been suggested or implied by several writers.[13,39]

In some cases, hypertension is probably due in part to stenosis of one or both renal arteries[39,41] or to coarctation of the aorta above the renal arteries, in addition to the mechanism (see above) which operates in the usual case of pulseless disease with involvement predominantly in the arch of the aorta.

The site of occlusion of the branches of the aortic arch may be several centimeters from the arch itself. In Nagoya, I reviewed the case of a 22-year-old female patient with obstruction of the right subclavian artery just beyond the origin of the vertebral artery.[18] The histologic change was typical of Takayasu's disease. The occluded segment was successfully replaced with a graft.

In one 20-year-old female patient with otherwise typical pulseless disease, the right pulmonary artery was totally occluded, and a second patient had multiple stenoses of pulmonary arteries in association with stenosis at the aortic arch.[14] In some autopsies the pulmonary artery and its main branches have shown histologic involvement.[9] Here is yet another feature which indicates more generalized involvement of large arteries in this disease.

Finally, one of the patients examined, a 20-year-old woman, had had signs and symptoms of arterial insufficiency in the left leg suggesting Buerger's disease. Birke, Fjrup and Olhagen[6] described a similar patient. What appears to be a distinct entity and what can probably be best called *the Buerger syndrome*[47] occurs relatively frequently in the Orient. However, undoubtedly the Buerger syndrome and Takayasu's disease are completely distinct, with little overlap in symptoms, signs, and other features (Table III).

Course and prognosis. The course and prognosis are features of the clinical description of pulseless disease which have not been well determined. Most of the patients are studied on only one occasion and are observed for only a short period of time. Most series include only cases of very severe involvement, and the cases are

*This patient will be described in the *Japanese Heart Journal* by Professor Hideo Ueda and his colleagues.

†One probable case of this type, that of a 20-year-old Korean woman with obstruction of the entire descending aorta by an intimal and [illegible] process and with low blood pressure in the left arm, was reviewed at the Presbyterian Medical Center, Chonju, Korea, through the courtesy of Dr. R. B. Dietrick.

usually detected late in the course of the disease. It would be highly desirable for someone with a large series of such cases to determine what has become of the patients after a certain interval of time and to make an attempt periodically to follow up a significant number. Obviously such information is essential to planning and evaluating treatment (see below).

In 1949 I first saw a 25-year-old white woman with an advanced form of the aortic arch syndrome. The disease may have had its onset when she was 7 years old. The carotid and right radial pulses were not felt. The left radial pulse was weak and inconstant. A continuous murmur in the vicinity of the left clavicle was interpreted as that of patent ductus arteriosus. The patient developed ventricular fibrillation during cardiac catheterization but was resuscitated after 45 minutes, during which time the circulation was maintained by open-chest cardiac massage. Recently the patient (who now lives in California) reported that she has been improving symptomatically in recent years, but she still cannot look up without developing severe dizziness. She cannot have a chest x-ray film taken in the usual manner with the chin elevated, and in the past she has fainted when such was attempted. She went through an attack of acute cholecystitis and a cholecystectomy uneventfully.

A second patient (R. B. 541885, a Negro woman) who was referred to previously[1] as probably having the young female arteritis type of aortic arch syndrome, was 21 years old when she had an illness characterized by pain and swelling in many larger joints and fever. Soon afterward, absence of the pulse in the left arm was incidentally discovered by her physician. Symptoms in the left arm began when she was 25 years old. At the age of 28 she was found to have a bruit above and below the left clavicle. Left dorsal sympathectomy was performed. When she was 31, similar symptoms began in the right arm, for which right anterior cervical sympathectomy was performed 2 years later. Sedimentation rates have been persistently elevated (Wintrobe 26-33 mm. per hour corrected) for the last 9 years. When seen recently at the age of 37 years she was remarkably well. Pulse and blood pressure were unobtainable in the right arm. Blood pressure was 110/90 mm. Hg in the left arm. A systolic bruit was still present in the left supraclavicular fossa. No signs of involvement of the carotids, femorals, or abdominal aorta were discovered.

Shown in Fig. 1 is an aortogram of a 36-year-old white woman (D. R., 990430) from South Africa who recently consulted me with a previously proposed diagnosis of Takayasu's disease. We concurred in the diagnosis because the sedimentation rate had been elevated persistently for at least 16 months and because the aortogram showed (1) mild segmental coarctation of the descending thoracic aorta, (2) segmental coarctation of the first part of the left common carotid artery, which more distally became wider although not so wide as its counterpart on the right, (3) generalized alteration of the left subclavian and vertebral arteries with a complete or nearly complete block of the left subclavian artery just after the origin of the left vertebral artery, and (4) fairly extensive development of collateral vessels, especially the transverse scapular artery on the left. The left arm was obviously smaller than the right and had weak or absent pulses. A systolic murmur in the left supraclavicular fossa became almost continuous with application of heat to the arm. Onset of the process may have occurred 10 years previously with the development of pain in the left side of the face. Ischemic symptoms in the arm had been present for 2 to 3 years. (We[3] described previously a young female patient in whom pain in the left side of the face was a leading symptom, and pulses were absent in the left arm, with normal carotid pulses.)

Etiology. Little more than speculation is possible in regard to etiology. Tuberculosis was suspected earlier mainly because of the nature of the histology. However, there is absolutely no specific evidence in support of the possibility of tuberculosis, although such has been sought. Currently most students of the disease are thinking in terms of an autoimmune basis.[52] Investigations along these lines might be profitable.

Case 3 of Lessof and Glynn[44] is of great interest. The patient, a 21 year-old white woman, had had absent pulses in branches of the aortic arch for at least a year and anastomotic vessels surrounded the right optic disc. At the age of 13 years she had had acute rheumatic fever which left her

Table III. A comparison of the Buerger syndrome and Takayasu's disease

	The Buerger syndrome	Takayasu's disease
Sex	Overwhelmingly male	Overwhelmingly female
Age of onset	20-40	10-30
Arteries involved	Intermediate and smaller ones of extremities	Great vessels
Veins involved	Often	Probably never



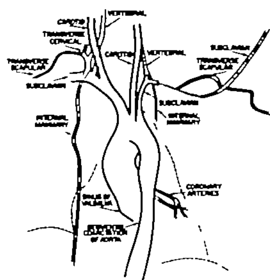


Fig 1 Aortogram (*left*) and outline drawing (*right*) which represent the significant findings. For description of patient (D R., 990430), see text Note (1) the mild but unequivocal segmental coarctation of the descending thoracic aorta, (2) the smaller size of the left common carotid and left subclavian arteries and branches e g vertebral and internal mammary arteries, (3) the narrow segment of the first part of the left common carotid which then becomes wider (4) the narrowing and possibly complete occlusion of the left subclavian artery just beyond the origin of the narrowed left vertebral, and (5) the dilatation of collateral channels on the left, especially the transverse scapular artery Very similar findings were described in Cases 1 and 4 of Edling and associates.[4]

with considerable aortic regurgitation. At the time of report, systemic lupus erythematosus was being treated with adrenocortical steroids the basis of the diagnosis was the following elevated sedimentation rate high globulin faintly positive Wassermann test with negative treponemal immobilization test and the presence of an antinuclear factor in the blood demonstrated by the method of Holborow and co-workers. The authors knew of no other case of systemic lupus erythematosus with the aortic arch syndrome involvement of smaller arteries is more familiar

Part of the riddle is this What is it about the environment and/or the constitution of the Oriental female which renders her relatively prone to this disease?

Treatment. Adrenocortical steroids and anticoagulants have been used with results which are difficult to interpret In most cases extensive obstructive disease is already present by the time the patient comes to medical attention The medical measures might be considered merely as preparatory and ancillary to surgical treatment. Endarterectomy and local resections with grafting have been performed with indifferent success. Apparently definitive surgical reconstruction of the aortic arch and its major branches has not been attempted in the Orient

Finally a comment on one of the clinical features which is most interesting from the point of view of medical history and medical sociology that is, the high frequency with which feeble or absent radial pulse is one of the presenting complaints of the Oriental patient with the aortic arch syndrome. Such was the case in over a third of the patients studied by Sano[7] The Western layman is sophisticated about matters such as appendicitis, herniated intervertebral disc and recently coronary occlusion If the Oriental layman is ill he is likely to feel his radial pulses. Taking the pulse is what taking the temperature is in a similar situation in Western experience In Chinese medicine taking the pulse is the principal and often sole, diagnostic method An extensive literature on the pulse dating from many centuries ago has accumulated[22] Most of it is probably totally worthless However in all the chaff there may be a few kernels of empirically discovered associations for

which a basis can be found in modern knowledge of hemodynamics. A story is told of a princess who was ill but could not be examined directly by the court physician because of the customs of the time. The resourceful physician had a string attached to the royal wrist and led to the courtyard where by feeling the end of the string he arrived at a diagnosis—right or wrong.

If the doctor who examines Oriental patients does not palpate at least both radial pulses he is in risk of being considered a quack. Patients with occlusive peripheral vascular disease who were studied during the visits to Japan and Korea[1] were greatly impressed by the fact that nine pulses on each side of the body were systematically tested!

In 1953 Ross and McKusick[2] speculated on what part the emphasis on pulses in Oriental medicine might have had in the early and frequent reporting of pulseless disease from Japan and China. It certainly played some role but in addition there is, equally certainly, a higher frequency of pulseless disease in the Orient than in the West.

REFERENCES

1. Benske R. Ein eigentümlicher Fall schwieliger Aortitis, Virchows Arch. path. Anat. 254 723 1925
2. Ross, R. S., and McKusick, V. A. Diminished or absent pulses in arteries arising from the arch of the aorta: the aortic arch syndrome. Arch. Int. Med. 92 701 1953
3. Shimizu, K., and Sano, K. Pulseless disease. J. Neuropath. & Clin. Neurol. 1:37 1951
4. Southworth, J. L., McKusick, V. A., Peirce, E. C., II, and Rawson, F. L., Jr. Ventricular fibrillation precipitated by cardiac catheterization. Complete recovery of the patient after 45 minutes. J.A.M.A. 143 717 1950.
5. McKusick, V. A. Cardiovascular sound in health and disease. Baltimore, 1958, Williams & Wilkins Company
6. Barker G. Ejrup B. and Olhagen, B. Pulseless disease. A clinical analysis of 10 cases, Angiology 8:433 1957
7. Sano, K., Tokyo University. Personal communication, March 1961
8. Sato, T. Ein seltener Fall von arterien Obliteration, Klin. Wchnschr. 17 1154 1938.
9. Oota, K. Ein seltener Fall von beiderseitigem Carotis-Subclavia-verschluss. Ein Beitrag zur Pathologie der Anastomosis peripapillaris des Auges mit fehlendem Radialpuls, T. Soc. path. Jap. 30:680 1940
10. Fukata, Kouza, and Kameya. Kyushu University. Personal communication, March 1961
11. Takayasu, U. A case with unusual changes of the central vessels in the retina. Acta Soc. Ophthalm. Jap. 12:554 1908.
12. Ohta, H., Kitamura, K., and Yamakawa, K. Two cases of pulseless disease. Resp. and Circ. 7:291 1959
13. Kim, C. S. Two cases of pulseless disease (the aortic arch syndrome). Med. Bull. Nat. Med. Center (Seoul) 1:67 1960
14. Kussmaul, A. Zwei Falle von spontaner allmählicher Verschliessung grosser Halsarterienstamme. Deutsches Klin. 24:461 1872
15. Koh, Torahiro. Takayasu disease: a condition with unusual systemic manifestations. J. Korean Med. Ass. 1:42, 1947
16. Yoshida, T., and Donomae, I. Osaka. Personal communication, March, 1961
17. Ask-Upmark, E. On the pulseless disease outside of Japan, Acta med. scandinav. 149 161 1954
18. Inadao, K., et al. Pulseless disease and atypical coarctation of the aorta, Resp. and Cir. 9 15 1961
19. Ask-Upmark, E., and Fajers, C. M. Further observations on Takayasu's syndrome. Acta med. scandinav. 155:275 1956
20. Danaraj, T. J., and Wong, H. O. Primary arteritis of abdominal aorta in children causing bilateral stenosis of renal arteries and hypertension, Circulation 20:856 1959
21. Shrikhare, P. V. Notes on a remarkable case of absence of pulsation in the arteries of the upper parts of the body. Indian J. Med. 2:326 1921
22. Savory, W. S. Case of a young woman in whom the main arteries of both upper extremities and of the left side of the neck were throughout completely obliterated. Med. Chir. T. 39:205 1856
23. Hume, E. H. The Chinese way in medicine. Baltimore 1940 The Johns Hopkins University Press
24. Black, D. M. Absence of pulse. Chinese M. J. 45:552, 1931
25. Caccamise, W. C., and Whitman, J. F. Pulseless disease: a preliminary case report. Am. Heart J. 44:629 1952
26. Brown, C. F. Absence of pulse: case of absence of pulse in both axillary, radial and carotid arteries while normal in the femoral and dorsalis pedis arteries. Chinese M. J. 43:269 1929
27. McKusick, V. A., and Harris, W. S. The Buerger syndrome in the Orient, Bull. Johns Hopkins Hosp. (in press)
28. Chang, H. T., Chang, A., and Chin, F. H. The pulseless disease, Chinese M. J. 71:63 1955
29. Jervell, A. Pulseless disease. Nord. med. 50 1272 1953.
30. Ask-Upmark, E. On the pathogenesis of the hypertension in Takayasu's syndrome. Acta med. scandinav. 169:465 1961
31. Ohta, H., Tokyo University. Personal communication, March, 1961

32. Wada, T. Tokyo University. Personal communication, March 1961.
33. Harbitz, F. Bilateral carotid arteritis, Arch. Path. & Lab. Med. 1:499, 1926.
34. Raeder, J. G. A case of symmetrical affection of the carotid with presenile cataract and glaucoma as well as cerebral atrophy. Klin. Monatsbl. Augenh. (Suppl.) 78:63, 1927.
35. Lewis, T., and Stokes, J. A curious syndrome with signs suggesting cervical arteriovenous fistula, with pulses of neck and arm lost. Brit. Heart J. 4:57, 1942.
36. Skipper, E., and Flint, F. J. Symmetrical arterial occlusion of upper extremities, head, and neck: a rare syndrome, Brit. M. J. 2:9, 1952.
37. Myers, J. D., Murdaugh, H. V., McIntosh, H. D., and Blaisdell, R. K. Observations on continuous murmurs over partially occluded arteries. An explanation for the continuous murmur found in the aortic arch syndrome. Arch. Int. Med. 97:726, 1956.
38. Maspetiol, R., and Teptas, J. N. Thrombosis of the large branches of the aortic arch in a young woman: relationships to multiple thromboising arteritis, Semaine hôp. Paris 81:2705, 1948.
39. Frøvig, A. G. Bilateral obliteration of the common carotid artery. Acta psychiat. et neurol., Suppl. 39, 1946.
40. Marinesco, G. and Kreindler, A. Oblitération progressive et complète des deux carotides primitives: accès épileptiques: considérations sur le rôle des sinus carotidiens dans la pathogénie de l'accès épileptique. Presse méd. 44:833, 1936.
41. Elliot, A. H., Umber, N. T., and Stone, C. S. Bilateral carotid sinus denervation in a patient having syncopal attacks and a congenital vascular anomaly. Report of an unusual case. Am. Heart J. 17:69, 1939.
42. Ask-Upmark, E., Uppsala. Personal communication, May 1961.
43. Martorell, F., and Fabré, J. El síndrome de obliteración de los troncos supra-aorticos, Medicina clínica (Barcelona) 2:26, 1944.
44. Lessof, M. H., and Glynn, L. E. The pulseless syndrome. Lancet 1:799, 1959.
45. Edling, N. P. G., Nyström, B., and Seldinger, S. I. Branchial arteritis in the aortic arch syndrome. A roentgen and differential diagnostic study. Acta radiol. 53:417, 1961.
46. Kwak, N. O., Chang, J. H., and Lee, S. H.: Pulseless disease: a report of three cases, Korean J. Int. Med. 3:79, 1960 (in Korean).
47. Sen, P. K., Bombay. Personal communication.
48. Misra, S. S., Prakash, S., and Agrawal, P. L. Pulseless disease (Takayasu's syndrome). Am. Heart J. 57:177, 1959.
49. Case records of the Massachusetts General Hospital #23-1961. New England J. Med. 264:671, 1961.
50. Sano, K.: Obstructive disease of the carotid arteries, with especial reference to angiitis, Medical Progress 37:236, 1961 (in Japanese).

The $R_{V_6}:R_{V_5}$ voltage ratio in left ventricular hypertrophy

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The electrocardiographic diagnosis of left ventricular hypertrophy (LVH) is a constant problem. Innumerable papers have been published on the subject and report widely differing results, especially in regard to the specificity of various criteria. One possible criterion which has escaped wide attention is the $R_{V_6}:R_{V_5}$ voltage ratio. The occurrence of greater R wave voltage at lead position V_6 than at V_5 in LVH was first suggested by Littmann[1] and found by Griep[2] to have been present in 25.5 per cent of a series of 200 cases of LVH which was proved at autopsy. In our patient material we have attempted to assess the frequency of this finding as well as its specificity for the electrocardiographic diagnosis of LVH.

Materials and methods

Thirty-five hundred consecutive electrocardiographic tracings obtained from 1,500 patients were reviewed for cases showing greater R wave voltage at the V_6 than at the V_5 position ($R_{V_6}:R_{V_5}$ ratio greater than 1). Analysis was restricted to tracings in which ventricular complexes in both the V_5 and V_6 positions were of similar unipolar derivation (qRs, qRS, or qR), in order to eliminate unusual locations of the transition zone due to such factors as pulmonary disease and myocardial infarction.

The chest x-ray films, clinical findings, and pathologic data for each patient were reviewed. LVH was considered to be present when there was unequivocal thickening of the left ventricle at necropsy and/or when the chest film, independently reviewed by the roentgenologist, provided unequivocal evidence of LVH.

Results

Thirty-nine patients (2.6 per cent) had an $R_{V_6}:R_{V_5}$ ratio greater than 1. Four of these were rejected because of associated marked leftward mediastinal shift (2), pectus cavum with cardiac displacement (1), and lack of either x-ray or necropsy data (1). The 34 cases retained revealed the following. (a) All 5 patients on whom an autopsy was performed had left ventricular hypertrophy. (b) Of the other 29 patients, 21 had chest films which were definitely positive for LVH. (c) Twenty of the 21 patients who had chest films which were positive had one or more disease states commonly associated with LVH—hypertensive heart disease, arteriosclerotic heart disease, rheumatic heart disease with mitral

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32. Wada, T., Tokyo University Personal communication, March 1961
33. Harbitz, F Bilateral carotid arteritis, Arch. Path. & Lab Med. 1:499 1926.
34. Raeder J G A case of symmetrical affection of the carotid with presenile cataract and glaucoma as well as cerebral atrophy Klin Monatsbl. Augenh. (Suppl.) 78:63 1927
35. Lewis, T and Stokes, J A curious syndrome with signs suggesting cervical arteriovenous fistula, with pulses of neck and arm lost, Brit Heart. J 4:57 1942.
36. Skipper E., and Flint, F J Symmetrical arterial occlusion of upper extremities, head, and neck a rare syndrome, Brit. M J 2:0 1952
37. Myers, J D., Murdaugh H V McIntosh H D and Blaisdell, R. K. Observations on continuous murmurs over partially occluded arteries. An explanation for the continuous murmur found in the aortic arch syndrome Arch. Int. Med. 97 726 1956
38. Maspetiol, R., and Taptas, J N Thrombosis of the large branches of the aortic arch in a young woman relationships to multiple thrombosing arteritis, Semaine hôp Paris 81:2705 1948.
39. Frøvig, A. G Bilateral obliteration of the common carotid artery Acta psychiat et neurol., Suppl. 39 1946.
40. Marinesco, G and Kreindler A. Oblitération progressive et complète des deux carotides primitives accès épileptiques considérations sur le rôle des sinus carotidiens dans la pathogénie de l'accès épileptique, Presse méd. 44:833, 1936
41. Elliot, A H., Ussher N T and Stone C. S. Bilateral carotid sinus denervation in a patient having syncopal attacks and a congenital vascular anomaly Report of an unusual case Am. Heart J 17:69 1939
42. Ask Upmark, E., Uppsala Personal communication May 1961
43. Martorell, F., and Fabré J El síndrome de obliteración de los troncos supra-aorticos, Medicina clínica (Barcelona) 2:26 1944
44. Lessof M H., and Glynn L. E. The pulseless syndrome Lancet 1:799 1959
45. Edling N P G Nyström, B and Seldinger S. I Branchial arteritis in the aortic arch syndrome. A roentgen and differential diagnostic study Acta radiol. 55:417 1961
46. Kwak, N O Chang, J H and Lee, S. H Pulseless disease a report of three cases, Korean J Int. Med. 3 79 1960 (in Korean)
47. Sen, P K Bombay Personal communication.
48. Misra S. S., Prakash, S., and Agrawal, P L.: Pulseless disease (Takayasu's syndrome) Am Heart J 57:177 1959
49. Case records of the Massachusetts General Hospital #23-1961 New England J Med. 261:671 1961
50. Sano, K. Obstructive disease of the carotid arteries with especial reference to angiitis, Medical Progress 37:236 1961 (in Japanese)

Effects of hyperventilation on systemic and coronary hemodynamics

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The electrical activity of the brain, as measured by the electroencephalogram undergoes marked changes during hyperventilation.[1,2] Since the changes are qualitatively the same as those which occur during hypoxia, and since pH[3] and carbon-dioxide content[4] change so rapidly during hyperventilation, it was postulated that these changes occurred from hypoxia due to the Bohr effect on hemoglobin.[4] When it became possible to measure cerebral blood flow, it was quickly established that cerebral blood flow decreased both in man[5] and experimental animals[6] and that the cerebral venous blood oxygen tension[7] and brain oxygen consumption decreased. It is well known that hyperventilation may be associated with electrocardiographic changes,[8-11] as well as changes in peripheral[12,13] and central venous pressure.[14,15] Cardiac output has been reported to remain essentially unchanged,[16] and to be changed unpredictably in dogs.[17] In man, it is agreed that hyperventilation increases total body oxygen consumption[18-21] and cardiac output is reported to be unchanged (on the basis of the ballistocardiogram),[5] variably increased,[22] and markedly increased.[23] The above-discussed chain of events in regard to the cerebral circulation and to the general systemic hemodynamics as well as the clinical symptoms[4] produced by hyperventilation have raised the question whether the coronary circulation is affected by hyperventilation, and if so whether the changes are in the same direction as those in the cerebral circulation.

Material and methods

The present study consisted of two portions, one of which was done in experimental animals and the other in man. The study in experimental animals was carried out in 28 mongrel dogs anesthetized by the administration of 3 mg. per kilogram of morphine sulfate subcutaneously, followed in 1 hour by injection of 12 mg. per kilogram of pentobarbital or 0.25 ml. per kilogram of a 50:50 mixture of veterinary Nembutal and Dial-urethane.* The early part of the series received the first of these anesthetics and the latter part the second since the anesthetized state seemed more stable with the Dial-urethane mixture. During the hour after administration of

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*Dial-urethane furnished through the courtesy of Ciba Pharmaceutical Products, Inc., Summit, N. J. [illegible] mg. of Dial, 400 mg. of monoethylurea, and 400 mg. of urethane per milliliter. [illegible] Nembutal [illegible] mg. of pentobarbital per [illegible]

the intravenous anesthetic, cardiac catheters were manipulated fluoroscopically into the pulmonary artery the coronary sinus and the right atrium and needles were placed percutaneously in either one or both femoral arteries. Cardiac output was determined 1 hour after the administration of the anesthetic by the Fick principle and coronary blood flow was determined by the nitrous-oxide saturation method Expired air was collected in a Tissot spirometer and analyzed for oxygen and carbon dioxide by the Scholander method Specimens of blood were collected in oiled heparinized syringes and analyzed for oxygen and carbon dioxide by the Van Slyke Neill method Analyses for nitrous oxide were done by the method of Orcutt and Waters. Blood gas tensions were estimated from the standard tables.[illegible] Pressures were measured with Statham strain gauges recording on either the Sanborn

Table I Systemic and coronary hemodynamic effects of hyperventilation in man

Catheterization number		Sex	Age (yr)	Surface area (M²)	Blood pressure (mm Hg) Mean arterial	Mean pulmonary arterial	Mean coronary sinus	Heart rate	Minute volume respiration (L/min)	Body O_2 consumption	CO_2 excreted
					Normals						
1.	C	M	58	1.95	102	18	10.0	98	6.0	208	170
	S				89	17	6.3	127	29.0	357	342
434	C	M	47	1.77	96	19	6.4	59	5.8	243	182
	S				84	14	6.1	67	20.2	292	244
459	C	F	28	1.58	89	9	4.7	90	3.0	186	131
	S				83	10	3.8	74	11.7	256	238
440	C	M	25	2.15	87	15	5.7	71	7.0	269	244
	S				82	16	5.5	85	26.2	386	420
463	C	M	35	1.87	88	15	3.6	81	4.5	235	162
	S				90	14	3.9	94	28.7	393	385
493.	C	M	26	1.76	91	15	6.3	89	5.3	261	188
	S				84	12	5.2	106	22.3	409	332
					Mitral Stenosis						
437	C	F	41	1.66	100	29	8.0	60	4.9	211	156
	S				91	20	3.3	72	12.9	285	198
436.	C	F	35	1.49	71	35	3.3	74	6.7	201	187
	S				70	24	2.7	73	10.5	249	232
487	C	F	41	1.73	94	30	5.3	74	5.1	214	177
	S				87	21	3.9	76	16.0	240	255
Average control (before) ±S.D					91±9	21±9	6.1±1.9	77±13	5.4±1.2	225±28	177±31
Average study (during) ±S.D					84±9	16±5	4.5±1.3	86±20	19.7±7.3	319±68	291±78
Per cent change					−7.7	−23.8	−26.2	+11.7	+264.8	+41.8	+66.1
S.E.M difference					1.599	1.532	0.566	4.230	2.351	16.792	21.706
p value <					0.01	0.05	0.05	0.1	0.001	0.001	0.001

Poly Viso or the Gilson Macropolygraph Mean pressures were determined by electrical integration of the pressure curve. Calculations were done by the usual formulas. Cardiac work was calculated as mean arterial blood pressure times cardiac output with appropriate constants for expression in kilogram-meters per minute In 9 animals, cardiac output was determined also by the Hamilton indicator dilution method utilizing indocyanine green as the indicator The indicator dilution curves were inscribed through a Gilford Model 103 IR densitometer on the direct writing Gilson Macropolygraph It was calibrated in each animal by dilutions of indocyanine green in the whole blood of the dog

Attempts to stimulate active hyperventilation in the dogs were unsatisfactory and for this reason passive hyperventilation was used Hyperventilation was ac

R Q	*Arterial O_2 content* (ml./100 ml of blood)	*Arterio-venous O_2 difference* (ml./100 ml of blood)	*Mixed venous CO_2 content* (ml./100 ml of blood)	*Mixed venous-arterial CO_2 difference* (ml./100 ml of blood)	*Coronary sinus O_2 content* (ml./100 ml of blood)	*Arterial-coronary sinus O_2 difference* (ml./100 ml of blood)	*Coronary sinus CO_2 content* (ml./100 ml of blood)	*Coronary sinus arterial CO_2 difference* (ml./100 ml of blood)
				Normal				
0.82	18.8	5.1	45.7	4.0	6.1	13.3	50.8	9.7
0.96	20.7	7.0	31.3	6.0	4.6	15.3	39.9	11.6
0.75	15.9	3.9	50.4	2.7	5.6	10.5	55.3	8.5
0.84	16.7	5.5	33.8	3.0	3.2	13.5	40.4	9.1
0.70	15.4	3.3	50.2	1.7	5.1	10.5	56.2	7.7
0.93	16.0	4.7	40.7	3.2	3.8	12.5	47.9	9.4
0.91	19.3	4.2	51.6	3.1	5.6	13.7	58.0	9.5
1.09	21.1	4.4	37.4	6.6	3.6	16.1	44.8	12.0
0.69	18.5	4.0	48.5	2.3	8.0	10.5	54.0	7.6
0.98	19.2	4.8	32.4	4.2	5.0	13.7	39.7	9.4
0.72	17.7	3.3	52.0	2.2	7.2	10.3	56.8	7.5
0.81	18.6	5.1	34.9	3.6	5.5	13.2	44.3	9.1
				Mitral Stenosis				
0.74	17.8	5.7	51.3	3.6	3.9	14.0	56.6	9.8
0.69	17.9	5.8	39.8	4.3	3.6	13.3	44.9	11.5
0.93	16.1	3.9	51.6	3.4	5.2	11.1	57.3	9.5
0.93	16.0	4.7	46.8	4.4	4.4	11.6	52.3	9.6
0.83	18.5	3.6	48.2	2.9	5.6	12.5	55.4	9.6
1.06	18.8	3.0	36.6	5.7	3.6	15.1	44.6	11.4
0.79±0.09	17.6±1.4	4.1±0.8	50.0±2.1	2.9±0.7	5.8±1.2	11.8±1.5	55.6±2.2	8.8±1.0
0.92±0.13	18.3±1.9	5.2±0.8	37.3±4.7	4.6±1.3	4.1±0.8	14.0±1.5	44.3±4.1	10.3±1.2
+16.5	+4.0	+26.8	−25.4	+58.6	−29.3	+18.6	−20.3	+17.0
0.037	0.231	0.222	1.260	0.337	0.2 2	0.293	1.029	0.242
0.01	0.01	0.01	0.001	0.001	0.001	0.001	0.001	0.001

complished in a few animals by intermittent positive pressure and in the others by the Stephenson Model 1600 Controlled Respiration Unit in view of the more physiologic effects of alternating positive and negative pressure.[31] Studies were alternated in the experimental animals so that in one half of them the control observations were made first, and in the other half the hyperventilation studies were made first. To minimize the effects of changes in intrathoracic pressure on hemodynamics, both the control and experimental observations were made with the respirator in use. Only the volume of ventilation was changed in the two studies. The large number of dogs was required because with the degree of hyperventilation obtained the respiratory quotient remained very high and hence the Fick output data were somewhat questionable. With the use of the nitrous-oxide curves from the coronary blood flow determination as a criterion the steady state was quite

Table I Systemic and coronary hemodynamic effects of hyperventilation in man—Cont'd

Catheterization number		Arterial hemoglobin	Arterial hematocrit	Arterial pH	Coronary sinus pH	Cardiac index	Left ventricular work index (Kg.M./min.)	Right ventricular work index (Kg.M./min.)	Total peripheral resistance (c.g.s.)
					Normals				
433.	C	15 2	47	7 39	7 36	2 1	2 9	0 5	1999
	S	15 9	49	7 56	7 54	2 6	3 2	0 6	1396
434	C	13 8	41		7 42	3 5	4 6	0 9	1231
	S	13 8	41			3 0	3 4	0 6	1264
439	C	12 8	40	7 46	7 39	3 6	4 3	0 4	1262
	S	12 7	39	7 69	7 62	3 4	3 9	0 4	1218
440	C	16 0	47	7 39	7 36	3 0	3 5	0 6	1086
	S	16 0	48	7 71	7 62	4 1	4 6	0 9	747
463	C	14 5	44			3 1	3 7	0 6	1197
	S	14 7	45			4 4	5 3	0 9	878
493.	C	14 6	45			4 5	5 6	0 9	920
	S	14 7	45			4 6	5 2	0 7	837
					Mitral Stenosis				
437	C	14 8	45	7 44	7 40	2 2	3 0	0 9	2160
	S	14 9	44	7 70	7 65	3 0	3 7	0 8	1460
436.	C	13 2	40	7 36	7 30	3 5	3 4	1 7	1101
	S	13 2	38	7 47	7 40	3 6	3 4	1 1	1056
487	C	13 4	43			3 4	4 4	1 4	1264
	S	13 6	44			2 8	3 3	0 8	1449
Average control (before) ±S.D.		14.3±1 0	44±3	7 41±0 04	7.36±.04	3.2±0 7	3 9±0 9	0.9 _0 4	1358 425
Average study (during) ±S.D.		14 4±1 1	44±4	7.63±0 11	7.57±.10	3.5±0 7	4 0±0.8	0.8±0.2	1147±278
Per cent change		+0 7	0	+3 0	+2 9	+9 4	+2.6	−11 1	−15.5
S.E.M. difference		0 078	0 425	0 036	0 029	0 227	0 318	0 113	97.883
p value <		0.3		0 01	0 01	0.3	0.8	0.5	0 1

satisfactory since the arterial curves rose rapidly to reach a steady plateau and the venous curves rose smoothly toward the same level The difference between the oxygen and carbon-dioxide content in inspired and expired air was so small however that a very minor error in the analysis of expired air became significant and produced unacceptable errors in calculated oxygen consumption and carbon dioxide release. Therefore, the Scholander data were not used in the dogs, and the only data accepted for cardiac output were those derived from the latter portion of the series utilizing the Hamilton method Furthermore the data on oxygen consumption and carbon-dioxide elimination in the dogs are calculated from the output as determined by the Hamilton indicator dilution method multiplied by the arteriovenous oxygen and carbon-dioxide difference.

In view of the known capacity of the dogs to endure marked hyperventilation

Cardiac R.Q	*Coronary blood flow* (ml./100 Gm./min.)	*Cardiac metabolic rate/O_2* (ml./100 Gm./min.)	*Cardiac metabolic rate/CO_2* (ml./100 Gm./min.)	*Coronary vascular resistance*	*Index of efficiency*	*Arterial CO_2 tension*	*Coronary sinus CO_2 tension*	*Coronary sinus O_2 tension*
				Normals				
0 56	129	17 2	12 5	0 79	0 17	36 8	43 2	18
1 21	63	9 6	7 2	1 44	0 33	18 2	26 5	11
0 81	92	9 7	7 8	1 04	0 47			
0 67	61	8 2	5 6	1 38	0 41			
0 3	146	15 3	11 2	0 61	0 28	35 9	47 8	18
0 76	102	12 5	9 6	0 81	0 31	18 1	24 7	17
0 69	58	7 9	5 5	1 50	0 44	43 2	51 7	17
0 75	61	9 8	7 3	1 34	0 47	15 8	24 2	9
0 72	87	9 1	6 6	1 01	0 41			
0 69								
0 73	148	15 2	11 1	0 61	0 37			
0 69	97	12 8	8 8	0 87	0 41			
				Mitral Stenosis				
0 69	44	6 2	4 3	2 27	0 48	35 0	45 0	13
0 75	49	7 3	5 6	1 86	0 49	16 0	2 8	9
0 86	61	6 8	3 8	1 16	0 50	43 1	57 5	19
0 83	64	7 4	6 1	1 09	0 46	33 1	43 0	16
0 77	111	13 9	10 7	0 85	0 32			
0 76	56	8 3	6 4	1 55	0 39			
0.73±.08	99±41	11.5±4.4	8 6±3 1	1.10± 56	0.38± 12	39 _4	50 3	17 _3
0 79± 16	*69±19*	*9.5±2.1*	*7 1±1 5*	*1.29± 35*	0 41± 06	20 7	28 8	11±3
+8.2	−30.3	−17 4	−17 4	+17 3	+7 9	−48 7	−44 0	1
0 076	10.332	1.171	0 900	0 137	0 024	2 693	2.247	
0 5	0 05	0 2	0 2	[illegible]	[illegible]	[illegible]	[illegible]	—

Table II Systemic and coronary hemodynamic effects of hyperventilation in the dog

Parameter	n	Rest	Study	% difference	S.E.M. difference	p value <
Heart rate	28	83	143	+72.3	7.075	0.001
Mean systemic arterial pressure (mm. Hg)	28	111	110	−0.9	1.553	0.5
Mean pulmonary arterial pressure (mm. Hg)	28	13	17	+30.8	0.586	0.001
Mean right atrial pressure (mm. Hg)	22	4.2	5.8	+38.1	0.316	0.001
Minute volume respiration (L./min.)	28	3.2	20.3	+534.4	1.175	0.001
Body oxygen consumption (ml./min.)	11	116	115	−0.9	5.897	0.9
Body carbon dioxide excreted (ml./min.)	11	75	139	+85.3	10.835	0.001
Body respiratory quotient	11	0.65	1.21	+86.2	0.067	0.001
Arterial oxygen content (ml./100 ml. blood)	28	17.0	18.6	+9.4	0.252	0.001
Mixed venous oxygen content (ml./100 ml. blood)	28	12.1	13.4	+10.7	0.467	0.01
Δ Arteriovenous oxygen difference (ml./100 ml. blood)	28	4.9	5.2	+6.1	0.312	0.4
Mixed venous carbon dioxide (ml./100 ml. blood)	28	44.0	31.6	−28.2	0.901	0.001
[illegible]ial carbon-dioxide content (ml./100 ml. blood)	28	40.7	25.9	−36.4	0.904	0.001
[illegible]enous-arterial carbon-dioxide (ml./100 ml. blood)	28	3.3	5.7	+72.7	0.276	0.001
Coronary sinus oxygen (ml./100 ml. blood)	28	4.2	4.1	−2.4	0.280	0.8
Δ Arterial-coronary sinus oxygen (ml./100 ml. blood)	28	12.6	14.4	+14.3	0.325	0.001
Coronary sinus carbon dioxide (ml./100 ml. blood)	28	50.9	36.0	−29.3	0.981	0.001

in order to dissipate heat,[17] it appeared that a species difference in the effects of hyperventilation might be present and that it might be desirable to study the problem also in man, in whom such respiratory efforts are poorly tolerated. To this end 9 human subjects were studied. Three of those studied had mitral stenosis, 1 had auricular fibrillation of unknown significance, and each of the other 5 was considered to be normal in so far as the cardiovascular system was concerned. Catheterization was done in the human subjects when they were in the fasting state without premedication. A concerted effort was made to keep the subject at ease throughout the procedure. Cardiac output was determined first with the catheter advanced into the pulmonary artery. The tip of the catheter was then withdrawn from the pulmonary artery and placed in the coronary sinus. Coronary blood flow was determined by the nitrous-oxide saturation method. Subsequently, the patient was asked to hyperventilate. After hyperventilation had been carried out for 5 to 10 minutes, the second determination of the coronary blood flow was made, when the state of the patient appeared to be quite steady and he manifested signs of hyperventilation with tingling of the fingers, dizziness, and weakness. Then, while hyperventilation was continued, the tip of the catheter was placed in the pulmonary artery and the second determination of cardiac output was made. The basic analytical procedures were the same with the human subjects as they were with the experimental animals, and the methods were the same, except that in all cases the Sanborn Poly Viso was used instead of the Gilson Macropolygraph. No indicator

dilution curves were recorded in man but since the degree of hyperventilation was less than that accomplished in the dogs, the difficulties with the respiratory quotient and the inspiratory-expiratory oxygen and carbon-dioxide differences were proportionately less. A uniform degree of cooperation in hyperventilation was not obtainable in all subjects, as is apparent in the data however again the steadiness of the hyperventilatory state was deduced to be satisfactory from the shape of the nitrous-oxide curves.

Results

The data from both studies are summarized in Tables I and II In the experimental animals the heart rate increased by 72 per cent ($p < 0.001$) whereas the mean systemic arterial blood pressure remained unchanged Mean pulmonary arterial blood pressure rose 30.8 per cent ($p < 0.001$) and mean right atrial blood pressure increased 38 1 per cent ($p < 0.001$) The minute volume of respiration increased 534 per cent ($p < 0.001$) Although the oxygen consumption did not change (calculated by multiplying the arterio-venous oxygen difference by the cardiac output as determined by the Hamilton indicator-dilution method) carbon-dioxide excretion (calculated in the same fashion) increased 85.3 per cent ($p < 0.001$) and the calculated respiratory quotient increased 86 2 per cent ($p < 0.001$) This should undoubtedly be designated the exchange ratio since it is presumed that the major portion of the change in respiratory quotient was due to depletion of tissue and body stores of carbon dioxide

Table II *Systemic and coronary hemodynamic effects of hyperventilation in the dog*—Cont d

Parameter	*n*	*Rest*	*Study*	*% difference*	*S.E.M difference*	*p value* <
Δ Coronary sinus-arterial carbon dioxide (mL/100 mL blood)	28	10 5	12 3	+17 1	0 366	0 001
Cardiac respiratory quotient	28	0 84	0 85	+1 2	0 021	0 7
Arterial hemoglobin (Gm./100 mL)	28	13 8	14 1	+2 9	0 161	0 02
Arterial hematocrit	28	43	43	—	0 495	—
Femoral arterial pH	28	7 26	7 62	+5 0	0 020	0 001
Coronary sinus pH	28	7 25	7 60	+4 8	0 017	0 001
Cardiac output (L./min.)	11	2 6	2 9	+11 5	0 167	0 2
Total peripheral resistance (c.g.s. units)	11	3891	3566	−8 4	176 7	0 1
Left ventricular work (Kg.M./min.)	11	4 1	4 6	+12 2	0 286	0 2
Right ventricular work (Kg.M./min.)	11	0 5	0 7	+40 0	0 056	0 01
Stroke volume (mL)	11	35	21	−40 0	1 732	0 001
Stroke work (Gm M./min)	11	56	33	−41 1	3 337	0 001
Coronary blood flow (ml /100 Gm /min.)	28	77	85	+10 4	4 898	0 2
Left ventricular oxygen usage (mL/100 Gm /min)	28	9 5	12 1	+27 4	0 651	0 001
Left ventricular carbon dioxide liberation (ml /100 Gm./min.)	28	7 9	10 2	+29 1	0 597	0 001
Coronary sinus oxygen tension (mm. Hg)	12	21	13	−33 3	1 171	0 001
Coronary vascular resistance (units)	28	1 59	1 43	−10 1	0 094	0 2
Index of efficiency	11	0 40	0 34	−15 0	0 023	0 02

rather than to such a marked change in metabolism of the body. The arterial oxygen content increased 9.4 per cent ($p < 0.001$) whereas mixed venous oxygen content increased 10.7 per cent ($p < 0.01$) and the arteriovenous oxygen difference was not changed significantly. Simultaneously there was a marked decrease in mixed venous carbon-dioxide content (−28.2 per cent, $p < 0.001$) and arterial carbon-dioxide content (−36.4 per cent, $p < 0.001$) with widening of the mixed venous-arterial carbon-dioxide difference (+72.7 per cent, $p < 0.001$). The coronary sinus oxygen content, on the other hand, did not change significantly, but because of the increase in the arterial oxygen content the arterial–coronary sinus oxygen difference increased (+14.3 per cent, $p < 0.001$). Because of the marked pH shift, the coronary sinus oxygen tension decreased markedly (−33.3 per cent, $p < 0.001$). Coronary sinus–arterial carbon-dioxide difference increased (+17.1 per cent, $p < 0.001$) and the coronary sinus carbon-dioxide content decreased (−29.3 per cent, $p < 0.001$) as did the carbon-dioxide tension ($p < 0.001$). The cardiac respiratory quotient did not change significantly. The cardiac output as calculated by the Hamilton indicator-dilution method did not change significantly, nor did the total peripheral resistance. Left ventricular work was unchanged but right ventricular work increased (+40.0 per cent, $p < 0.01$). The coronary blood flow was essentially unchanged whereas cardiac oxygen usage and carbon-dioxide liberation increased (+27.4 and +29.1 per cent, respectively, $p < 0.001$). Coronary vascular resistance did not change significantly nor did the hemoglobin or hematocrit. Because the left ventricular oxygen consumption increased more than the left ventricular work, its calculated efficiency was reduced (−15 per cent, $p < 0.02$). The femoral arterial and coronary sinus pH increased 5.0 and 4.8 per cent, respectively ($p < 0.001$). Stroke volume and stroke work were both significantly reduced (−40.0 and 41.1 per cent, respectively, $p < 0.001$).

The corresponding data for hyperventilation studies in 9 human subjects indicated a slight but insignificant increase in cardiac rate accompanied by a significant reduction in mean blood pressure in the systemic arteries (−7.7 per cent, $p < 0.01$), pulmonary artery (−23.8 per cent, $p < 0.05$) and coronary sinus (−26.2 per cent, $p < 0.05$). The minute volume of respiration was increased (+264.8 per cent, $p < 0.001$) and the body oxygen consumption was increased (+41.8 per cent, $p < 0.001$) with carbon-dioxide excretion increased still more (+66.1 per cent, $p < 0.001$). The calculated respiratory quotient, or preferably exchange ratio, of the body increased by 16.5 per cent ($p < 0.01$). The arterial oxygen content increased slightly but significantly (+4.0 per cent, $p < 0.01$) whereas the mixed venous oxygen difference did not change and the arteriovenous oxygen difference rose (+26.8 per cent, $p < 0.01$). Mixed venous carbon-dioxide content, on the other hand, decreased (−25.4 per cent, $p < 0.001$) with an even greater decrease in the arterial carbon-dioxide content (−30.6 per cent, $p < 0.001$) and tension (−48.7 per cent, $p < 0.01$) and significant widening of the venous-arterial carbon dioxide difference (+58.6 per cent, $p < 0.001$). The coronary sinus oxygen content decreased (−29.3 per cent, $p < 0.001$) with widening of the arterial–coronary sinus oxygen difference (+18.6 per cent, $p < 0.001$) and the coronary sinus carbon dioxide content decreased (−20.3 per cent, $p < 0.001$) with widening of the coronary sinus–arterial carbon-dioxide difference (+1?.0 per cent, $p < 0.001$). The cardiac index increased by 9.4 per cent, which was not significant. There were insignificant changes in cardiac work and total peripheral resistance. Coronary blood flow varied considerably from subject to subject, but in the total group it decreased 30.3 per cent ($p < 0.05$) and there were variable but insignificant decreases in left ventricular oxygen consumption and carbon-dioxide liberation. Calculated left ventricular efficiency did not decrease, and the hemoglobin and hematocrit were not changed significantly. However, the pH increased in both the femoral artery (+3.0 per cent, $p < 0.01$) and the coronary sinus (+2.9 per cent, $p < 0.01$) and as a manifestation of these changes in pH as well as the decrease in oxygen and carbon-dioxide con

tent of coronary sinus blood the coronary sinus oxygen tension decreased 35.3 per cent ($p < 0.01$) whereas the coronary sinus carbon-dioxide tension decreased by 44.0 per cent ($p < 0.001$)

Discussion

It is apparent from a survey of the results of the two sets of data that there are some rather marked discrepancies. It is believed that the increase in pulmonary arterial and right atrial pressures in the experimental animals is due to the effects of the respirator. These animals were maintained on the respirator throughout the hyperventilation and the normal ventilation periods in order to minimize the effect of the positive pressure phase of the respirator however it seems probable that the rise in pressure inside of the chest was greater during the hyperventilation than during the resting ventilation and that this pressure was transmitted from the lung through the elastic heart walls into the right atrium and the pulmonary artery. In the human subjects the strong inspiratory motion of the chest wall produced negative intrathoracic pressure, which was transmitted to the pulmonary artery and right atrium and apparently accounted for the decreased pressure within these structures. A similar decrease in right atrial pressure has been found by others,[14] but there is considerable discussion as to whether the effective distending pressure actually increases or decreases, and it has been concluded by Eckstein and Hamilton [14] as well as Coleridge and Linden [15] that an increase occurs when allowance is made for the increased negativity of intrathoracic pressure. The failure of oxygen consumption to increase in the dogs as it did in man is also to be expected, since the dogs were passively hyperventilated, whereas in the man the act of hyperventilation requires considerable expenditure of energy [16-21]

In regard to coronary blood flow it does not appear that the difference between the two groups is so readily explained. In the dogs the coronary blood flow tended to remain the same or to rise slightly whereas in the human subjects the coronary blood flow fell variably but significantly. This may very well be a species difference between the two since hyperventilation is a normal mechanism in the dog for the dissipation of heat [22] but overbreathing is poorly tolerated in man. That the dog can increase his coronary blood flow during marked hyperventilation is shown by his response to hyperthermia.[22]

There can be no doubt that as postulated previously [6] there were significant decreases in blood oxygen and carbon dioxide tension particularly in the coronary sinus as a result of hyperventilation. Since coronary sinus oxygen tension must, in part reflect the myocardial oxygen tension it seems clear that myocardial oxygen and carbon-dioxide tension fall with hyperventilation. In the human subjects the combination of reduced coronary blood flow and decreased coronary sinus blood oxygen content and tension seems particularly significant. It has been shown that hyperventilation with 100% oxygen produces less change in the electrocardiogram the electroencephalogram and the state of awareness than does hyperventilation with air or 10 per cent oxygen.[4] Furthermore it has been shown that the administration of Pro-Banthine or the ingestion of 5 Gm of potassium bicarbonate and 5 Gm. of potassium acetate will prevent the changes in the T waves of the electrocardiogram which occur with hyperventilation.[11] It seems most unlikely that such alkalinizing salts would increase blood oxygen tension. Sodium bicarbonate increases coronary blood flow in the dog [23] but whether it does so in man is not known and no data concerning potassium bicarbonate are available. It is conceivable that the total blood carbon-dioxide content is an important factor in maintaining coronary blood flow as it apparently is in the maintenance of the cerebral flow [24] and indeed inhalation of carbon dioxide is reported to increase coronary blood flow in the dog [25] Pro-Banthine might be expected to have sympathicomimetic effects on the coronary circulation, and hence be associated with increased coronary blood flow similar to the known effect of coronary denervation,[27] and administration of atropine.[28] In the absence of information concerning cardiac oxygen consumption an increase in coronary blood flow does not insure higher myocardial oxygen tension

however and more specific knowledge is required

It is of interest that the coronary blood flow in these human subjects decreased in such a variable fashion. Thus there was essentially no change in 3 subjects, whereas in 5 subjects the decrease was considerable. What, if any clinical significance this has is not clear In 2 of the subjects in whom coronary blood flow did not change significantly there was limited hyperventilation because the subjects did not cooperate fully This leaves only 1 subject in whom the respiratory response was satisfactory but coronary blood flow did not decrease. No explanation for this discrepancy is offered however a variable pattern of response to hyperventilation has been reported previously[10,17,20] and does not seem to have been accounted for adequately That acute hyperventilation may cause release of catecholamines has been suggested by the report that phentolamine prevents the increase in right atrial distending force which normally occurs.[14] If such were indeed the case prolonged hyperventilation such as that in the present study might give results different from those of acute hyperventilation.[20]

Conclusions

1 Hyperventilation has been studied in dogs and in man and determinations of coronary and systemic hemodynamics have been made

2 Cardiac output increased slightly but insignificantly in both groups of experimental subjects.

3 Although coronary blood flow did not change in experimental animals it was significantly reduced by hyperventilation in the human subjects.

4 During hyperventilation the coronary sinus oxygen and carbon-dioxide tensions were reduced considerably and presumably the myocardial oxygen tension was lowered

The authors regret that this study was conducted over such a long period of time that it is not possible to acknowledge properly the assistance of all of those who helped with the various procedures involved.

REFERENCES

1 Davis, H and Davis, P A. The electrical activity of the brain: its relation to physiological states and to states of impaired consciousness, Assoc. for Res in Nervous and Mental Diseases 19:50, 1939

2. Gibbs, F A., Gibbs, E. L., and Lennox, W G Electroencephalographic response to overventilation and its relation to age, J Pediat. 23:497 1943

3. Shock, N W and Hastings, A. B Studies of acid base balance of the blood. IV Characterization and interpretation of displacement of the acid base balance, J Biol. Chem 112:239 1935.

4. Brassfield C. R., and Behrmann, V G A correlation of the pH of arterial blood and urine as affected by changes in pulmonary ventilation, Am. J Physiol. 132:272 1941

5 Engel, G L., Ferris, E. B., and Logan, M Hyperventilation analysis of clinical symptomatology Ann. Int. Med 27:683 1947

6. Carryer H M Tissue anoxia resulting from respiratory alkalosis, Proc. Staff Meet. Mayo Clin. 22:456, 1947

7 Kety S. S and Schmidt, C F The effects of active and passive hyperventilation on cerebral blood flow cerebral oxygen consumption, cardiac output, and blood pressure of normal young men, J Clin. Invest. 25 107 1946

8. Malette, W Cerebral anoxia resulting from hyperventilation, Surg Forum 9:208, 1958

9 Barker P S., Shrader E. L and Ronzoni, E. The effects of alkalosis and of acidosis upon the human electrocardiogram, Am. Heart J 17 169 1939

10. Thompson, W P The electrocardiogram in the hyperventilation syndrome Am Heart J 25:372, 1943

11 Wasserburger R. H., Siebecker K. L., and Lewis, W C. The effect of hyperventilation on the normal adult electrocardiogram, Circulation 13:850, 1956.

12. McDowall, R. J S. The effect of carbon dioxide on the circulation. Part I J Physiol. 70:301 1930

13. Eckstein, J W Hamilton, W K. and McCammond, J M Pressure volume changes in the forearm veins of man during hyperventilation, J Clin. Invest. 37:956 1958.

14. Eckstein, J W., and Hamilton, W K. Changes in transmural central venous pressure in man during hyperventilation J Clin. Invest. 37:1537 1958.

15 Coleridge, J C. G and Linden, R. J The variations with respiration in effective right and left atrial pressure in the dog, J Physiol 145:482 1959

16. Roome, N W The cardiac output in hyperventilation by external alternating pressure Am. J Physiol. 104 142, 1933.

17 Brown, E. B J : Physiological effects of hyperventilation, Physiol. Rev 33:445 1953.

18. McKerrow C. B and Otis A. B Oxygen cost of hyperventilation, J Appl. Physiol. 9:375 1956.

19 Campbell, E. J M., Westlake, E. K., and Cherniack, R. M The oxygen consumption and efficiency of the respiratory muscles of young male subjects, Clin. Sc. 18:55, 1958.

20. Fritts, H. W Jr., Filler J Fishman, A. P., and Cournand, A. The efficiency of ventilation during voluntary hyperpnea studies in normal subjects and in dyspneic patients with either chronic pulmonary emphysema or obesity J Clin. Invest. 38:1339 1959
21 Murray J F Oxygen cost of voluntary hyperventilation, J Appl. Physiol. 14 187 1959
22. Burnum, H. F Hickam, J B and McIntosh, H. D The effect of hypocapnia on arterial blood pressure, Circulation 9:89 1954
23 Gleason, W L., Berry J N Mauney F M and McIntosh, H D The hemodynamic effects of hyperventilation, Clin. Res. 6:127 1958.
24. Maloney J V., Affeldt, J E., Sarnoff S. J., and Whittenberger J L.: Electrophrenic respiration. IX. Comparison of positive pressure breathing and electrophrenic respiration on the circulation during hemorrhagic shock and barbiturate poisoning, Surg Gynec. & Obst. 92:672, 1951.
25. Rahn, H., and Fenn, W O A graphical analysis of the respiratory gas exchange, Washington, D C., The American Physiological Society Chart VII 1955.
26. Peters, J P and Van Slyke, D D Quantitative clinical chemistry Vol I Interpretations, Baltimore, 1931, The Williams & Wilkins Company
27 Maxwell, G. M., Castillo, C. A., Crumpton, C. W., and Rowe, G. G. Hyperthermia systemic and coronary circulatory changes in the intact dog, Am. Heart J 58:854 1959
28. Maxwell, G. M., Rowe, G. G Afonso, S., Crumpton, C. W., and Castillo, C. A. The effect of sodium bicarbonate upon the general and cardiac hemodynamics and metabolism of the intact dog (Abstract) Clin. Res. 7:387 1959
29 Schieve J F., and Wilson, W P The changes of cerebral vascular resistance of man in experimental alkalosis and acidosis, J Clin Invest. 32:33, 1953
30. Feinberg, H Gerola A., and Katz, L. N Coronary flow and myocardial oxygen consumption in hypercapnea, Fed. Proc. 17:45 1958.
31 Brachfeld, N., Monroe, R. G and Gorlin, R. Effect of pericoronary denervation on coronary hemodynamics, Am. J Physiol. 199:174, 1960
32. Gorlin, R. Studies on the regulation of coronary circulation. I. Atropine-induced changes in cardiac rate, Am. J Med. 25:37 1958.

Effect of postural changes on cardiac and renal function in hypertensive subjects

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It is generally accepted that in essential hypertension the cardiac output is normal.[1,3] Nevertheless recently some authors have found high values in both the juvenile[4] and adult forms of hypertension.[5,6]

With regard to renal function it has been demonstrated that the renal blood flow is usually decreased, especially in the advanced stages, and that the glomerular filtration rate either remains within normal limits or falls less than the renal blood flow, which thus implies an increase in the filtered fraction.[9] Concerning the excretion of water and electrolytes, it has been reported that hypertensive subjects excrete a greater quantity of water, chloride and sodium under basal conditions[10] and especially after loads.[11,12]

In normal subjects change from the horizontal to the semivertical standing or sitting positions is followed by a fall in cardiac output,[1,16] renal blood flow,[17] and excretion of water, chloride and sodium.[17,18] It is accepted that hemodynamic changes created by postural changes elicit reflex mechanisms which start from the pressoreceptors and volume receptors and which bring humoral factors into play. These tend to re-establish equilibrium and very probably participate in the changes in *renal function mentioned above.*

Bearing in mind the possible existence of high cardiac output with changes in the distribution of blood and alterations in the excretion of water and electrolytes, we thought it timely to study in these patients the general and renal hemodynamic changes caused by postural changes.

This investigation is of particular interest if one takes into account the fact that in hypertensive subjects the readjustment of the pressoreceptors to abnormal pressure on the one hand, and the early presence of sclerosis of the renal vessels on the other, may modify the renal and general hemodynamic responses caused by postural changes.

Material and methods

Eleven hypertensive subjects who were without evidence of cardiac or renal failure were selected for study. None of them showed any known cause of hypertension. When they arrived at the laboratory they were made to lie down on a tilting x-ray table and given 500 ml. of water to drink. Additional urinary loss of water was re-

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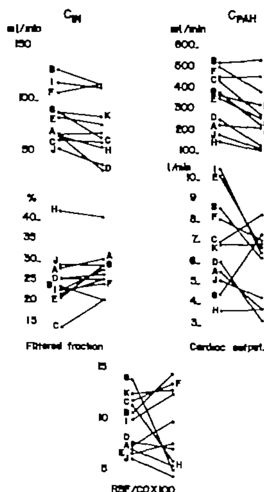


Fig 1 Change in C_{IN}, C_{PAH}, filtered fraction, cardiac output, and RBF/CO × 100 during postural changes in hypertensive subjects.

placed by an equivalent amount of fluid An adequate diuresis was thus maintained throughout the experiment. As soon as the subjects had been placed in position an indwelling multieyed catheter was placed in the bladder a polyethylene tube in the axillary vein through an antecubital vein and a Cournand needle in the brachial artery After an adequate priming dose an infusion of inulin and sodium para aminohippurate (PAH) in normal saline was started at a constant rate of 2 ml. per minute, and maintained throughout the experiment. Once diuresis became stable which took about 2 hours, the bladder was emptied and a control period of from 7 to 10 minutes was started after which the bladder was again emptied residual urine was expelled by air The patients were then placed in a semivertical position of 45 degrees, and after half an hour the bladder was again emptied and another period of the same duration was again started In the middle of each period samples of blood were taken and the cardiac output was measured by the dye-dilution technique using T 1824 The dye was injected in the axillary vein and blood samples were taken every 2 seconds from the brachial artery Samples of diluted plasma were read in a Beckman DU spectrophotometer Values were calculated according to the formulas devised by Hamilton.[19] The concentration of inulin [20] PAH [21] chloride [22] sodium and potassium (by flame photometry) was determined in every sample of blood and urine. From

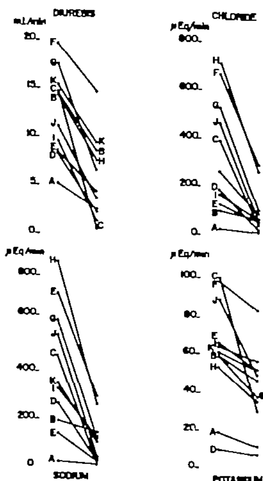


Fig 2 Change in diuresis and the excretion of chloride, sodium, and potassium during

these data renal blood flow glomerular filtration rate, and excretion of electrolytes were calculated

Results

A summary of results is given in Table I and Figs. 1 and 2.

Cardiac output evaluated as cardiac index was normal or in the lower normal limit in 4 subjects in the upper normal limit in another 4 and definitely high in the other 3 The postural change caused a fall in 7 subjects an increase in 2 and no significant change in the other 2 The trend of the changes was in no way related to the initial value

The renal blood flow calculated from clearance of PAH (C_{PAH}) and the hematocrit, was low in 9 subjects and in the lowest normal limit in 2 Postural change provoked a fall in 9 subjects, and no appreciable change in 2

There was no relation between the fall in the cardiac output and the renal blood flow In fact in the 7 subjects in whom there was a fall in the cardiac output in only 5 was there a drop in the renal blood flow and in 2 it was unchanged. On the

Table I Effect of postural changes on cardiac and renal function in hypertensive subjects

Case	Position	Time (min sec.)	Urine: Volume (ml./min.)	Cl (µEq/min.)	Na (µEq/min.)	K (µEq/min.)	C_{IN} (ml./min.)	C_{PAH} (ml./min.)	Filtered fraction	CO (L./min.)
A (3 yr)	Supine	14	5 14	36	26	18 5	69	242	0 28	5 66
	Tilted	14	2 71	8	3	11 6	69 2	219	0 31	3 89
B	Supine	10′	14 5	109	199	60	129	531	0 24	8 89
	Tilted	8	8 75	65 6	146	46	116	541	0 21	6 42
C	Supine	9′30″	14 6	395	468	100	65 7	450	0 14	7 07
	Tilted	12′15	1 48	52	23	30	60	280	0 21	8 46
D	Supine	11	8 18	196	263	10 1	68 6	265	0 25	6 09
	Tilted	10′43	2 33	25 6	39	7 1	32 8	126	0 26	3 18
F	Supine	14	8 28	124	141	66 2	82 8	366	0 22	10 8
	Tilted	12′30″	4 28	60	59	51 3	77 2	263	0 29	6 81
F	Supine	10′30″	19 8	673	736	99	106	458	0 23	8 20
	Tilted	12′15	14 8	281	281	83	116	464	0 25	7 10
G	Supine	10′	17 6	528	607	60	87 5	373	0 23	4 5
	Tilted	9′57	6 7	116	127	38	65 2	234	0 28	7 4
H	Supine	11′23	14 3	754	870	53	67 7	151	0 45	3 71
	Tilted	9′26	5 3	255	273	35	52	129	0 40	3 86
I	Supine	9′38	9 76	175	336	64	117	524	0 22	10 7
	Tilted	9′8	1 36	336	120	56	102	397	0 25	6 55
J	Supine	12	11 2	470	560	89	53	190	0 28	7 28
	Tilted	8′25	3 08	66 5	69	49	37	130	0 28	6 98
K	Supine	7 17	15 38	277	356	61	88	388	0 22	8 22
	Tilted	7′30″	9 33	88	102	52	84	330	0 25	4 33

C_{IN}: Clearance of inulin. C_{PAH}: Clearance of sodium para-aminohippurate. CO: Cardiac output. CI: Cardiac index. RBF: Renal blood

other hand in the 4 subjects in whom the cardiac output either did not change or rose, the renal blood flow decreased.

The ratio of renal blood flow to cardiac output was uniformly low it oscillated between 6 5 and 14 per cent. Because of the lack of correlation between the variations in the renal blood flow and the cardiac output during postural changes, the relationship between these changed in different ways. The ratio rose in 6 subjects, but decreased slightly in 3 and markedly in the other 2. The 2 subjects in whom the fall was the greatest were precisely those in whom the cardiac output rose when they changed to a semivertical position There was no direct relationship between the initial value of the renal blood flow and the extent of the fall in the ratio of renal blood flow to cardiac output For instance the maximum fall in this ratio was registered in Case G with a low renal blood flow of 632 ml whereas in Case B with a high flow (925 ml per minute) the ratio rose instead of falling

Glomerular filtration rate, determined by clearance of inulin (C_{IN}) was normal in 3 subjects and low in 8 Postural changes

CI (L./min./M²)	RBF (ml./min.)	RBF/CO ×100	Plasma Cl (mEq./L.)	Plasma Na (mEq./L.)	Plasma K (mEq./L.)	Blood pressure (mm. Hg) Systolic	Blood pressure (mm. Hg) Diastolic	Blood pressure (mm. Hg) Mean	Renal resistance (dynes/sec./cm.⁻⁵)	Peripheral resistance (dynes/sec./cm.⁻⁵)	Hematocrit
2 91	410	7 2	107	140	3 8	200	115	155	30 213	2 185	41
2 00	382	9 8	107	140	3 9	180	115	145	30 336	2 979	42 7
5 66	925	10 7	104	137	3 7	200	98	142	11 921	1 276	42 6
4 07	936	14 5	104	137	3 7	196	105	152	11 270	1 643	42 2
4 11	805	11 4	103	141	3 6	234	140	174	16 228	1 966	44
4 93	465	5 50	102	141	3 6	210	126	153	26 268	1 445	43 5
4 26	473	5 83	104	144	3 6	190	125	154	25 802	2 200	44 3
2 22	223	7 01	104	144	3 5	177	123	143	51 249	3 593	43 5
3 02	704	6 5	108	139	4 4	206	139	161	18 277	2 192	48
3 18	519	7 6	108	139	4 4	187	133	153	20 456	1 787	49
4 58	965	11 6	106	142	4 0	219	141	166	13 750	1 604	52 5
3 97	976	13 6	105	142	3 9	171	106	126	10 311	1 404	52 5
2 36	632	14 0	104	138	3 8	240	156	110	19 727	2 770	41
3 89	403	5 4	104	138	3 8	234	156	110	30 936	1 684	42
2 31	263	7 08	102	137	3 4	222	150	105	45 581	3 231	42 5
2 41	229	5 93	103	137	3 2	189	138	114	52 349	3 105	43 5
6 20	1 075	10 0	106	138	3 3	221	163	127	12 118	1 216	51 3
3 78	810	12 4	107	138	3 5	185	145	117	14 306	1 774	51 0
4 10	447	6 14	105	141	4 4	252	176	157	31 824	1 954	42 5
3 94	302	4 32	104	140	4 2	252	200	168	52 927	2 289	43 0
3 14	652	12 5	107	143	3 9	180	132	96	16 200	2 020	40 5
2 60	564	13 0	107	145	4 2	174	117	84	16 600	2 164	41 5

caused a fall in 8 subjects and a slight increase in 1. No appreciable changes were noted in the 2 other subjects. When the subjects were recumbent the filtered fraction was normal in 1 subject and high in the others. When the subjects were in the semivertical position it increased in 6, decreased in 3, and remained unchanged in 2.

When compared with a number of normotensive subjects who were studied by us under identical conditions,[1] the hypertensive subjects showed a greater tendency toward higher urinary excretion of water and salt. In 3 subjects the diuresis exceeded 15 ml. per minute and in 5 the excretion of sodium exceeded 420 μEq per minute; these were the highest figures reached by normal subjects.

The change to the semivertical position determined in all of the subjects studied a definite reduction in the excretion of water, chloride, and sodium. Excretion of potassium also fell, although not so consistently or markedly.

Discussion

The high average figures for cardiac output found in 7 hypertensive subjects agrees with the results obtained by other authors. Moreover, high values in hypertensive subjects, as compared to the values in normal subjects, were obtained in a simultaneous study carried out in this laboratory using Hamilton and/or Fick's technique with previous psychological training and serial determination of oxygen consumption.[25]

Since in this latter study it was found that the increase in cardiac output evidenced by some of the hypertensive subjects coincided with increased oxygen consumption, the possibility exists that the increase in the cardiac output may be due to the fact that satisfactory basal conditions can hardly be achieved in these subjects. This does not seem unlikely in the present study in view of the complexity of simultaneous measurement of cardiac and renal function. With reference to this point it should be noted that the conditions of these studies were rigorously checked. We are inclined, therefore, to consider that both factors, increase in oxygen consumption and cardiac output, are rather characteristic of these patients and are related to their psychic constitution or perhaps to other factors as yet undetermined.

As we expected, the renal blood flow and the ratio of renal blood flow to cardiac output were low in nearly all of the subjects studied; this finding would indicate renal ischemia. The lack of correlation between the variations in the renal blood flow and the cardiac output suggests that *the fall in the renal blood flow produced* by the semivertical position of the subject is due to two different mechanisms acting simultaneously: (1) fall in the cardiac output and (2) renal vasoconstriction with decrease in the ratio of renal blood flow to cardiac output. Balint[26] recently denied this last mechanism on the basis of direct measurement of the renal blood flow in dogs subjected to hemorrhagic shock or dehydration. This author maintains that the data obtained by other authors under similar conditions are due to the fact that during periods of oliguria renal clearance gives false low values, and he considers that a diuresis of not less than 1 ml. per minute is indispensable for the values to be accepted.[27] In our experiments an adequate diuresis was assured by previous water load. Thus, the fall in the ratio of renal blood flow to cardiac output in some of our patients may be interpreted as indicative of a true elective renal vasoconstriction. With respect to this it is of interest to note that some hypertensive subjects who had a significantly decreased renal blood flow could reduce this even more by renal vasoconstriction.

In regard to the mechanism which causes the latter, the increase in the cardiac output with simultaneous decrease in the renal blood flow and increase in the filtered fraction, which was observed in 2 subjects, would appear to indicate a catecholamine type of response, in spite of the statement of Hickler and associates[7] that the change from the horizontal to a semivertical position produces no increase in the secretion of epinephrine and norepinephrine in hypertensive subjects who, on the other hand, already have high levels.

The fall in the excretion of sodium

and chloride which was observed by us in all subjects confirms the findings of earlier investigators and our data make it possible to draw some conclusions with respect to the possible mechanisms brought into play. Some authors, among them Wesson[22] attribute these sharp falls in the excretion of chloride and sodium to small falls in the glomerular filtration rate which although not detectable by the methods available are nevertheless, able by themselves to account for the changes observed. On the other hand other authors such as Epstein and associates,[24] on the basis of experiments carried out while the glomerular filtration rate was kept constant by an infusion of isotonic albumin when the subjects were standing conclude that the fall in the excretion of chloride and sodium under these conditions is independent of any changes in the filtration. Nevertheless, re-evaluation of their results shows an actual fall in the glomerular filtration which although minimal and well within the technical error could explain per se the fall in the excretion of sodium and chloride. On the other hand the importance of the tubular factor has recently been stressed by the finding of increased production of aldosterone during standing.[21-23] That this is not the only factor in play is shown by the fact that in patients with Addison's disease the excretion of chloride and sodium also falls during postural changes.[24] Mills and co-workers[25] have recently found that the inhibitory action of spironolactone on the decrease in excretion of chloride and sodium during standing is greater in those subjects with lesser falls in the rate of glomerular filtration which would suggest that both factors act with different intensity according to the subjects.

Our results throw some light on this question. The rate of glomerular filtration did not change in 2 of our hypertensive subjects, but rose in a third. These data reveal that in these cases the drop in the excretion of chloride and sodium was independent of the glomerular filtration rate because, even though the methods used to measure them were not very accurate, the fact that in one case the C_{In} was greater when the subject was in the semivertical position excludes a [illegible] the filtration rate in these circumstances. It is difficult to explain why there was no fall in these cases. It may be due to previous water loading which maintained an adequate circulatory volume.

Vander and associates[24] basing their opinions on earlier papers of Barger[27] related the retention of water and sodium in cases of cardiac failure to an increase in the filtered fraction and therefore there is the possibility that this mechanism also plays some role during postural changes in those cases in which no fall in glomerular filtration was registered. Possibly this rise in the filtered fraction was due to an increase in the production of renin consequent to the decrease in the renal blood flow. It is known that renin also influences the excretion of sodium.

The data given indicate that the fall in the excretion of chloride and sodium when the subject is in the semivertical position does not depend on a single factor but on the interaction of many factors which act differently in different subjects.

Summary

The cardiac output (CO) renal blood flow (RBF) glomerular filtration rate (GFR) and excretion of electrolytes were studied in a group of 11 hypertensive subjects who were placed first in a horizontal position and then in a semivertical position of 45 degrees.

The average figures of the CO tended to be high. The RBF and the RBF/CO ratio were low which was considered to be indicative of renal ischemia. The GFR was either normal or low and the filtered fraction was high in all cases. The basal excretion of water and salt also tended to be high.

The change to a semivertical position elicited a fall in the CO in 7 subjects, a rise in 2 and a lack of significant change in the other 2. The RBF fell in 9 subjects and remained unchanged in 2. There was no relationship between the variations in the CO and the RBF so that the RBF/CO ratio showed variable changes. It rose slightly in 7 subjects and fell in 4. In 2 of these the fall was pronounced. This is interpreted as indicating that some hypertensive subjects with frankly diminished RBF are [illegible]

vasoconstriction to the stimulus of postural changes.

The excretion of chloride sodium and water fell in a normal way during change of posture.

REFERENCES

1. Weiss, S., and Ellis, L. The quantitative aspects and dynamics of the circulatory mechanism in arterial hypertension Am. Heart J 5:449 1929
2. Starr I Collins, L. H and Wood, F C Studies of the basal work and output of the heart in clinical conditions, J Clin Invest. 12 13 1933
3. Goldring, W and Chasis, H Hypertension and hypertensive diseases New York 1944 Commonwealth Fund p 44
4. Bolomey A. A., Michie, A J Michie, C Breed E. S., Schreiner G E., and Lawson, H. D Simultaneous measurement of effective renal blood flow and cardiac output in resting normal subjects and patients with essential hypertension, J Clin. Invest. 28 10 1949
5. Taylor S. H Donald, K. W and Bishop J M Circulatory studies in hypertensive patients at rest and during exercise Clin. Sc. 16:351 1957
6. Fejfar Z. Juvenile hypertension Presented in the Symposium on Pathogenesis of Essential Hypertension, Prague, May 23-28, 1960
7. Werko, L. Presented in the discussion of the Symposium on Pathogenesis of Essential Hypertension, Prague, May 23-28, 1960
8. Brod J Fencl, V Hejl, Z and Jirka, J Circulatory changes underlying blood pressure elevation during acute emotional stress (mental arithmetic) in normotensive and hypertensive subjects, Clin Sc 18:269 1959
9. Goldring W Chasis H Ranges H. A and Smith, H W Effective renal blood flow in subjects with essential hypertension, J Clin. Invest 20:637 1941
10. Cottier O T Renal hemodynamics water and electrolyte excretion in essential hypertension. *In* Essential Hypertension, an International Symposium Berlin 1960 Springer Verlag p. 66.
11. Birchall, R. Tuthill, S. W Jacobs, W S. Trautman, W J and Findley T Renal excretion of water sodium and chloride. Comparison of the response of hypertensive patients with those of normal subjects, patients with specific adrenal or pituitary defects and normal subjects primed with various hormones, Circulation 7:258, 1953
12. Green, D M Weddell, H G Wald, M H and Learned B The relationship of water and sodium excretion to blood pressure in human subjects, Circulation 6:619 1952
13. Taquini A. C Plesch S., Capris, T and Badano, A A Some observations on water and electrolyte metabolism in essential hypertension, Acta cardiol. 11:109 1956.
14. Baldwin, D S Biggs, A. W Goldring, W., Hulet, W H., and Chasis H Exaggerated natriuresis in essential hypertension Am. J Med. 24:893 1958.
15. McMichael, J and Sharpey Schafer E P : Cardiac output in man by a direct Fick method Effect of posture, venous pressure changes, atropine and adrenaline Brit. Heart J 6:33 1944
16. Stead E A. Warren J V Merrill, A. J and Brannon F S. The cardiac output in male subjects as measured by the technique of right atrial catheterization. Normal values with observations on the effect of anxiety and tilting J Clin Invest. 24:327 1945
17. Brun, C. Knudsen, E. O E., and Raaschou, F The influence of posture on the kidney function The fall of the diuresis in the erect posture Acta med. scandinav 122:315 1945
18. White H L., Rosen, I T Fischer, S. S., and Wood, G H The influence of posture on renal activity Am J Physiol. 78 185 1926
19. Pearce M L. and Newman E. Some postural adjustments of salt and water excretion, J Clin Invest. 33 1089 1954
20. Hamilton W F Moore, J W Kinsman J M and Spurling, R. G Studies on the circulation IV Further analysis of the injection method and of changes in hemodynamics under physiological and pathological conditions, Am. J Physiol. 99:534 1932
21. Schreiner G E Determination of inulin by means of resorcinol, Proc Soc. Exper & Biol. Med 74 117 1950
22. Smith H W Finkelstein N Aliminosa L., Crawford B and Graber M : The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man J Clin. Invest. 24:388 1945
23. Scribner B H Bedside determination of chloride a method for plasma, urine and other fluids and its application to fluid balance problems, Proc. Staff Meet. Mayo Clin. 25:209 1950
24. Villamil, M F Fermoso, J D de la Riva, I J Aramendia, P and Taquini A. C Unpublished observations
25. Taquini A. C Valmitjana, V Aramendia, J and Fermoso, J D Unpublished data.
26. Balint, P Le débit rénal au cours des états d'hypotension Excerpta Medica, International Congress Series 29:28, 1960
27. Balint, P Personal communication
28. Hickler R. B Hamlin J T and Wells R. E. Plasma norepinephrine response to tilting in essential hypertension Circulation 20:422, 1959
29. Wesson, L. G J : Glomerular and tubular factors in the renal excretion of sodium chloride Medicine 36:281 1957
30. Epstein, F H Goodyer A. V N Lawrason, F D and Relman A. S. Studies of the antidiuresis of quiet standing the importance of changes in plasma volume and glomerular filtration rate J Clin Invest 30:63 1951
31. Muller A. F Manning E. L., and Riondel, A. M Diurnal variation of aldosterone related to position and activity in normal subjects and patients with pituitary insufficiency An Inter

national Symposium on Aldosterone, Boston 1958, Little, Brown & Company p. 111

32. Bartter F. C., Biglieri, E. G., Pronove P., and Delea, C. S. Effects of changes in intravascular volume on aldosterone secretion in man. An International Symposium on Aldosterone, Boston, 1958, Little, Brown & Company p. 100.
33. Gowenlock, A. H., Mills, J. N., and Thomas, S. Acute postural alterations in aldosterone output in man, J Physiol 143:9 1958
34. Rosenbaum, J. D., Papper S., and Ashley M. M.: Variations in renal excretion of sodium independent of change in adrenocortical hormone dosage in patients with Addison's disease, J Clin. Endocrinol. & Metab 15:1459 1955
35. Mills, J. N. Thomas S., and Williamson, K. S. Altered renal tubular function in the standing human subject, Excerpta Medica, International Congress Series 29:59 1960
36. Vander A. J., Malvin R. L., Wilde, W. S., and Sullivan L. P. Re-examination of salt and water retention in congestive heart failure. Significance of renal filtration fraction Am J Med. 25:497 1958.
37. Barger A. C. The pathogenesis of sodium retention in congestive heart failure, Metabolism 5:480 1956.

The effect of intracardiac acetylcholine infusion upon right heart dynamics in patients with rheumatic heart disease studied during exercise

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Recent studies of vasomotor activity in the pulmonary vascular bed of human beings have resulted in the modification of the previously held concept of this bed as a passive vascular conduit.[1-19] Investigations which employed intracardiac infusion of acetylcholine†[19] have demonstrated pulmonary vasodilatation during such infusions, although the limited magnitude of the vasodepressor response of the pulmonary artery at rest has created doubt as to the clinical significance of this phenomenon.[19] The purpose of the present study is to determine the effect of intracardiac infusion of acetylcholine during steady-state exercise conditions in patients with rheumatic heart disease and mitral stenosis. The increment in pressure in the pulmonary artery under these conditions might provide a more suitable medium for the demonstration of significant vasodilator activity in the pulmonary artery.

Methods and materials

Catheterization of the right side of the heart was performed with a double or triple-lumen catheter. Acetylcholine chloride† was infused at a constant rate via the proximal lumen of a double-lumen catheter or via the middle lumen of a triple-lumen catheter into the outflow tract of the right ventricle, or via the proximal lumen of the triple-lumen catheter into the right atrium.

A Cournand needle was used for systemic arterial cannulation. Cardiac output was estimated by the Fick principle during open-circuit determination of oxygen consumption. Blood and gas analyses for oxygen and carbon dioxide were performed by the Van Slyke and the micro-Scholander methods, respectively. Multiple determinations of pressures in the right side of the heart and in the systemic arteries and cardiac output were made during the first 9 to 10 minutes of exercise. Infusion of acetyl-

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Table I Physical characteristics and diagnoses in 20 patients with rheumatic heart disease

Date	Catheterization number	Sex	Age (yr)	B.S.A. (M²)	Diagnosis	Dosage of acetylcholine mg/min
April 1 1958	192	M	25	1.92	Rh.H.D., E.H., M.S., minimal A.I., N.S.R.—IIC	0.5
April 12, 1958	195	M	28	1.91	Rh.H.D., E.H., A.I., A.S., M.S., M.I., N.S.R.—IB	0.5
May 1 1958	201	M	35	1.80	Rh.H.D., E.H., M.S., M.I., A.F.—IIIC	0.5
May 12 1958	202	M	37	2.10	Rh.H.D., E.H., A.S., A.I., T.S., N.S.R.—IB	1.5
May 26 1958	205	F	49	1.49	Rh.H.D., E.H., M.S., minimal A.I., A.F.—IIC	1.5
June 5, 1958	208	M	34	1.98	Rh.H.D., E.H., A.S., A.I., M.S. N.S.R.—IB	1.5
June 30 1958	216	F	44	1.57	Rh.H.D., E.H., M.S., A.S.? A.I., N.S.R.—IIC	2.25
July 8 1958	218	M	49	1.89	Rh.H.D., E.H., M.S., M.I., A.F.—IIC	2.25
Sept. 8, 1958	226	F	52	1.66	Rh.H.D., E.H., M.S., M.I., A.F.—IIC	2.25
Nov 10, 1959	353			1.66	Restudied 14 mo. later	6.0
Sept. 11 1958	228	M	50	1.89	Rh.H.D., E.H., A.S., A.I.—IIC	2 .5
Nov 21, 1958	249	M	33	1.73	Rh.H.D., E.H., M.S., M.I., A.I.? A.S., A.F.—IIC	2 .5
Dec. 9 1958	258	M	39	1.99	Rh.H.D., E.H., M.S., A.S., N.S.R.—IIC	2.25
Dec. 15, 1958	260	F	24	1.60	Rh.H.D., E.H., M.I., A.I., N.S.R.—IIC	2.25
Feb. 3 1959	269	F	34	1.49	Rh.H.D., E.H., M.S., A.I., atrial flutter—IIC	2 .5
Mar 11 1959	283	M	37	1.72	Rh.H.D., E.H., M.S.—IIC	3 -
June 16, 1959	313	M	42	1.75	Rh.H.D., E.H., M.S., minimal A.I. N.S.R.—IIC	6.0
Sept. 1 1959	327	M	49	1.9	Rh.H.D., E.H., M.I., N.S.R.—IB	6.0
Sept. 15 1959	333	M	40	1.67	Rh.H.D., E.H., M.S., minimal A.I., N.S.R.—IIC	9.0
Sept. 29 1959	339	M	40	1.64	Rh.H.D., E.H., M.S., minimal A.I., N.S.R.—IIC	6.0
April 6 1960	403	M	31	1.69	Rh.H.D., E.H., M.S., minimal A.I., N.S.R.—IB	6.5

Rh.H.D.: Rheumatic heart disease. E.H.: Enlarged heart. M.I.: Mitral insufficiency. M.S.: Mitral stenosis. A.S.: Aortic stenosis. T.S.: Tricuspid stenosis. N.S.R.: Normal sinus rhythm. A.F.: Atrial fibrillation. A.I.: Aortic insufficiency.

choline at a constant rate was then initiated as exercise continued and measurements of flow and pressure were repeated. The diagnoses, vital statistics and dosages of acetylcholine for the 21 studies in 20 patients are listed in Table I. In catheterizations numbered 192, 195 and 201 acetylcholine was infused into the right atrium. In all subsequent studies it was infused into the right ventricular outflow tract. The dosage level of acetylcholine was increased progressively as the study progressed in order to determine whether the drug was more effective in producing pulmonary vasodilatation at the higher rates of administration. All patients were digitalized prior to cardiac catheterization.

Results

The data are reported in three groups: (1) control mean pressure in the pulmonary artery less than 20 mm. Hg., (2) between 20 and 50 mm. Hg. and (3) more than 50 mm. Hg. Six studies were performed in the first group, 10 in the second, and 5 in the third (Tables II and III). Pressures in the systemic arteries were not altered by the infusion of acetylcholine in any of the three categories.

The data for the subjects who had a mean pressure in the pulmonary artery of less than 20 mm. Hg are outlined in Table IIA. Of the various parameters studied the only significant alteration was in the systolic *pressure of the pulmonary artery*, $0.02 > p > 0.01$. The absolute decrease in systolic pressure was of minimal magnitude, about 2.5 mm. Hg.

In the second group of 10 studies significant decreases were noted in systolic, diastolic, and mean pressures of the pulmonary artery, $0.01 > p > 0.001$, $0.02 > p > 0.01$ and $p < 0.001$, respectively. *The absolute changes were 7, 3.5 and 3.5* mm. Hg respectively. A decrease in minute ventilation, $0.01 > p > 0.001$, was also observed. The other experimental parameters were unchanged.

In the third group, mean pressure in the pulmonary artery of more than 50 mm Hg, no significant changes in pressure, flow or gas exchange data were noted.

*The over-all statistical summary is out*lined in Table III.

Table IIA. Hemodynamic and cardiac output data during exercise in patients with rheumatic heart disease (right heart catheterization)

Catheterization number		Pulmonary artery S/D mean	Brachial artery S/D mean	Ventricular rate per min.	Cardiac index (L./min./M² B.S.A.)	O_2 Consumption (ml./min./M²)	A-V difference (vol. %)	R	Stroke volume (ml./beat)	Arterial oxygen saturation (%)	Minute ventilation (L./min./M²)
A. Pulmonary Artery Mean Pressure Less Than 20 mm. Hg											
195	C	24 9 15	155 76 103	76	3 73	230	6 2	80	92	96	7 54
	Ac	20/7 9	150/73 102	79	3 99	263	6 6	85	96	98	7 50
16	C	39/14 19	181/79 104	119	3 06	269	8 8	88	40	97	10 34
	Ac	39/15 [illegible]	[illegible] 8/81 112	128	3 34	334	10 0	95	41	99	11 67
60	C	20/7 11	110/60 79	103	3 19	203	6 4	1 00	50	98	9 00
	Ac	18/8 11	115/62,85	106	3 27	206	6 3	90	50	98	7 81
315	C	20/9 13	127/68 91	80	3 53	230	6 5	88	77	99	7 10
	Ac	16/8 11	125/66,90	8	3 59	228	6 4	85	81	97	6 45
327	C	23 10 15	164/82,110	89	3 72	251	6 8	89	81	96	7 86
	Ac	21/8,12	160/79 106	93	3 69	265	7 2	93	76	97	7 60
403	C	27/12 18	128/72 95	84	2 78	200	7 2	89	56	97	7 76
	Ac	23/12,18	129/74,99	92	3 22	231	6 9	90	60	94	7 35
Mean	C	26/10 15	144/73,98	93	3 34	231	6 98	890	66	97 2	8 27
	Ac	23/10 14	143/73 99	96	3 52	253	7 23	897	67	97 2	8 06

C, Control. Ac, During infusion of acetylcholine.

Table IIB. Hemodynamic and cardiac output data during exercise in patients with rheumatic heart disease (right heart catheterization)

Catheterization number		Pulmonary artery S/D mean	Brachial artery S/D mean	Ventricular rate per min.	Cardiac index (L./min./M² B.S.A.)	O_2 Consumption (ml./min./M²)	A-V difference (vol. %)	R	Stroke volume (ml./beat)	Arterial oxygen saturation (%)	Minute ventilation (L./min./M²)
B. Pulmonary Artery Mean Pressure of 20-50 mm. Hg											
201	C	6[illegible] 31 43	113 4,8[illegible]	83	2 16	207	9 6	77	47	95	8 09
	Ac	6[illegible] 33 44	119 80,88	93	2 19	221	10 1	8[illegible]	43	99	7 74
203	C	36 21,27	164/74,111	81	2 79	204	7 3	80	72	97	7 36
	Ac	32, 19,24	161/71 105	81	3 17	223	7 1	83	83	97	6 75
205	C	58/24,35	145/79 104	83	2 65	228	8 6	93	47	96	10 75
	Ac	43/20,31	154 85 111	8[illegible]	2 75	235	8 5	93	48	97	9 05
226	C	44/22,34	182/101 139	107	2 68	240	9 0	8	42	94	9 62
	Ac	49/19,30	175/93 132	104	2 74	236	8 6	84	44	9[illegible]	9 24
228	C	31/15,22	186/52,101	82	3 77	273	7 3	99	87	97	11 63
	Ac	29/14,20	183 57 110	84	3 67	271	7 4	93	84	96	11 60

C, Control. Ac, During infusion of acetylcholine. Table is continued at top of page 89.

Table IIB *Hemodynamic and cardiac output data during exercise in patients with rheumatic heart disease (right heart catheterization)*—Cont d

Catheterization number		Pulmonary artery S/D mean	Brachial artery S/D mean	Ventricular rate per min	Cardiac index (L./min./M² B.S.A.)	O_2 Consumption (ml./min./M²)	A V difference (vol. %)	R	Stroke volume (ml./beat)	Arterial oxygen saturation (%)	Minute ventilation (L./min/M²)
					B Pulmonary Artery Mean Pressure of 30-50 mm. Hg						
258	C	38/15,25	119/62,85	73	2 89	193	6 7	77	79	98	7 83
	Ac	31/14,21	109/57,80	75	2 72	189	6 9	87	72	97	6 8
269	C	41/22,28	143/74,96	84	2 53	209	8 3	85	45	98	6 93
	Ac	26/13,21	122/61,88	78	2 76	209	7 7	85	53	94	6 45
283	C	42/23,27	145/90,102	99	2 56	208	8 1	79	45	97	5 26
	Ac	27/14,21	140/86,100	107	2 66	227	8 6	79	43	97	4 83
339	C	29/14,20	131/64,95	70	3 31	232	7 1	90	77	97	9 00
	Ac	24/12,17	133/65 91	69	3 20	212	6 7	93	77	93	8 59
353	C	44/24,34	180/104,140	110	2 55	226	8 9	81	38	97	6 85
	Ac	40/19,30	176/97 133	105	2 68	223	8 3	84	42	96	6 45
Mean	C	43/21,30	151/77 106	87	2 79	220	8 09	841	58	96 6	8 33
	Ac	36/18,26	147/75 104	88	2 86	225	7 99	871	59	96 4	7 74

C: Control. Ac: During infusion of acetylcholine.

Table IIC *Hemodynamic and cardiac output data during exercise in patients with rheumatic heart disease (right heart catheterization)*

Catheterization number		Pulmonary artery S/D mean	Brachial artery S/D mean	Ventricular rate per min.	Cardiac index (L./min./M² B.S.A.)	O_2 Consumption (ml./min./M²)	A V difference (vol. %)	R	Stroke volume (ml./beat)	Arterial oxygen saturation (%)	Minute ventilation (L./min/M²)
					C. Pulmonary Artery Mean Pressure More Than 50 mm. Hg						
192	C	102/50,69	120/69,84	90	3 72	259	7 0	81	79	96	9 56
	Ac	100/50,68	117/65,83	96	3 91	280	7 2	88	78	97	9 72
208	C	90/44,57	140/63 92	81	2 82	217	7 7	93	69	95	8 77
	Ac	82/38,53	133/62,91	90	2 84	207	7 4	94	63	94	8 33
218	C	118/50 70	157/74,97	84	2 43	277	11 4	94	55	93	10 55
	Ac	112/51 66	147/74,91	81	2 85	288	10 1	93	67	89	10 94
249	C	127/63 75	129/82,93	112	2 17	224	10 3	79	34	92	11 60
	Ac	136/62 78	128/80,93	113	2 16	223	10 3	81	33	95	8 26
333	C	78/44,55	139/75,97	84	3 02	223	7 4	90	60	95	7 11
	Ac	72/42,53	130/76,96	128	5 12	221	4 3	99	67	78	9 75
Mean	C	103/50,65	137/73 93	90	2 83	240	8 76	874	59	94 2	9 52
	Ac	100/49,64	131/71 91	101	3 38	243	7 86	910	62	90 6	9 40

C. Control. Ac: During infusion of acetylcholine.

Table III

		Pulmonary artery			Brachial artery		
		S	*D*	*M*	*S*	*D*	*M*
A	Mean control	25.5	10.2	15.2	144.2	72.8	97.8
	Mean Ac	22.8	9.7	13.7	142.8	72.5	99.0
N = 6	Mean change	−2.7	−0.5	−1.5	−1.3	−0.3	+1.2
	Significance of change	.02>p>.01	.5>p>.4	.3>p>.2	.5>p>.4	.8>p>.7	.6>p>.5
B	Mean control	42.5	21.1	29.5	150.8	77.3	105.9
	Mean Ac	35.6	17.7	25.9	147.2	74.9	103.8
N = 10	Mean change	−6.9	−3.4	−3.6	−3.6	−2.4	−2.1
	Significance of change	.01>p>.001	.02>p>.01	p<.001	.3>p>.2	.3>p>.2	.4>p>.3
C	Mean control	103.0	50.2	65.2	137.0	72.6	93.0
	Mean Ac	100.4	48.6	63.6	131.0	71.4	90.8
N = 5	Mean change	−2.6	−1.6	−1.6	−6.0	−1.2	−2.2
	Significance of change	.5>p>.4	.3>p>.2	.3>p>.2	.05>p>.02	.3>p>.2	.1>p>.05

N, Number of studies.

Discussion

Fritts and Cournand[2] have clearly discussed the problem of assessment of pulmonary vasomotor activity using pharmacologic agents. In addition to pulmonary vascular tone, other physiologic parameters must be considered. These include rate of pulmonary blood flow, heart rate, pressure in the left atrium, constriction or dilatation in the systemic circulation, extravascular pressure within the alveoli and thorax, and central blood volume.

We did not note significant changes in cardiac index, heart rate, or systemic arterial pressure after intracardiac infusion of acetylcholine during exercise. Fritts and associates[10] have shown that intracardiac infusion of acetylcholine in normal subjects did not alter central blood volume during inhalation of room air and hypoxic gas mixtures. Infusion of acetylcholine in the right ventricle did not alter the mean pressure in the left atrium in 13 patients studied during combined catheterization of the right and left sides of the heart.[11] Evidence of bronchospasm was not noted during the infusion of acetylcholine in these patients with rheumatic heart disease. Any observed fall in the pressure in the pulmonary artery can therefore be interpreted as evidence for active pulmonary vasodilatation. The minimal decreases in pressure in the pulmonary artery which were observed in these patients at various levels of pressure and during infusion of acetylcholine at varied rates suggest that acetylcholine does not have a potent vasodilator effect on the pulmonary artery. The alterations in pressure which were observed in the pulmonary artery during continued exercise after the infusion of acetylcholine are of little if any clinical significance.

Summary

Intracardiac infusion of acetylcholine into the right atrium or right ventricle during steady-state exercise in 20 patients with rheumatic heart disease resulted in only minimal alterations in the pressure in the pulmonary artery. The vasodilator effect of acetylcholine on the pulmonary artery under these conditions is minimal and of little or no clinical significance.

REFERENCES

1. Marshall, R.: The physiology and pharmacology of the pulmonary circulation, Prog. Cardiovasc. Dis. 1:341, 1959.
2. Fritts, H. W., Jr., and Cournand, A.: Pulmo-

Ventricular rate	*Cardiac index*	*O_2 consumption*	*A-V difference*	*R*	*Stroke volume*	*Arterial oxygen saturation*	*Minute ventilation*
91 83	3 34	230 5	7 0	0 89	66 0	97	8 26
96 00	3 52	252 8	7 2	0 90	67 3	97	8 06
+4 2	+0 2	+22 3	+0 3	+0 01	+1 3	0 0	−0 20
1>p>.05	.9>p>.8	1>p>.05	.4>p>.3	.9>p>.8	.5>p>.4	—	.6>p>.5
87 2	2 8	221 0	8 1	0 84	57 9	97	8 33
88 2	2 9	224 6	8 0	0 87	58 9	96	7 74
+1 0	+0 1	+2 6	− 1	+0 03	+1 0	−0 2	0 59
.6>p>.5	.3>p>.2	.6>p>.5	.5>p>.4	1>p>.05	.6>p>.5	.8>p>.7	.01>p>.001
90 2	2 8	240 0	8 8	0 87	59 4	94	9 51
101 6	3 4	243 8	7 9	0 91	61 6	90	9 40
+11 4	+0 5	+3 8	−0 9	+0 04	+2 2	−3 6	−0 11
.3>p>.2	.3>p>.2	.6>p>.5	.3>p>.2	.27>p>.1	.6>p>.5	.4>p>.3	p>.9

nary circulation, New York, 1959 Grune & Stratton, Inc., p. 62.

3. Halmagyi, D F Role of the autonomous nervous system in the genesis of pulmonary hypertension in heart disease, J Chron Dis. 9:525 1959
4. Patel, D J Lange, R. S., and Hecht, H. H. Some evidence for active constriction in the human pulmonary vascular bed, Circulation 18:19 1958.
5. Semler H. J Shepherd J T and Wood, E. H. The role of vessel tone in maintaining pulmonary vascular resistance in patients with mitral stenosis, Circulation 19:386 1959
6. Shepherd, J T Edwards, J E Burchell, H. B., Swan, H J C., and Wood, E. H Clinical, physiologic, and pathologic considerations in patients with idiopathic pulmonary hypertension, Brit. Heart J 19 70 1957
7. Harris, P Influence of acetylcholine on the pulmonary arterial pressure, Brit. Heart J 19:272, 1957
8. Wood, P Besterman, E. M., Towers, M. K., and McIlroy M. B The effect of acetylcholine on the pulmonary vascular resistance and left auricular pressure in mitral stenosis Brit. Heart J 19:279 1957
9. Soderholm, B and Werkö, L. Acetylcholine and the pulmonary circulation in mitral valvular disease, Brit Heart J 21 1 1959
10. Fritts, H W J Harris, P Clauss, R. H Odell, J E and Cournand A. The effect of acetylcholine on the human pulmonary circulation under normal and hypoxic conditions, J Clin. Invest. 37:99 1958.
11. Shepherd, J T., Semler H J Helmholz, H F and Wood, E. H Effects of infusion of acetylcholine on pulmonary vascular resistance in patients with pulmonary hypertension and congenital heart disease, Circulation 20:381 1959
12. Wood, P Pulmonary hypertension with special reference to the vasoconstrictive factor Brit. Heart J 20:557 1958
13. Samet, P Bernstein, W H Fernandez, L and De Victoria, W The effect of intracardiac acetylcholine infusion upon right heart dynamics in patients with rheumatic heart disease studied at rest, Am. J Cardiol (In press.)
14. Samet, P Bernstein, W H Litwak, R. S., and Fernandez, L. The effect of intracardiac acetylcholine infusion upon left heart dynamics in patients with rheumatic heart disease Brit. Heart J (In press.)

Use of death rates to evaluate cardiovascular screening tests

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When society faces a health problem of increasing magnitude, research into all methods of control is necessary and worth while. Diseases of the cardiovascular system, which caused 903,270 deaths (54 per cent of all deaths) in the United States in 1959, form such a problem. This group of diseases is the foremost cause of death in most of the advanced countries.

Enormous resources have been used to attack this problem, and few can complain that the research effort is inadequate. However, most research has aimed at the primary prevention of cardiovascular disease—seeking the etiological factors responsible for the various disease processes. This direction of attack is undoubtedly the more satisfying to physicians, but it is impossible to predict how soon practical control measures will evolve.

It would seem wise, therefore, to place some effort and funds into the relatively neglected aspect of secondary prevention—the detection and treatment of disease at the earliest possible stage. This control method is intellectually less satisfying, since the cardiovascular system is already damaged and the task is one of repair while the etiology of the disease remains unknown. Nevertheless, secondary prevention may soon provide useful control methods, since considerable strides have already been made despite its relative neglect.

Cardiovascular disease is treated only when the patient or his physician recognizes the need for medical care. Since much cardiovascular disease passes through a prolonged asymptomatic phase, an abundant need for treatment is unmet in the population of the United States. Thus multiple screening has been devised as a method of secondary prevention to separate persons with this need, without requiring the total adult population to be examined periodically by physicians.

Multiple screening uses two or more tests to sort out persons who probably have abnormalities from those who probably do not. Its immediate aim is to refer for medical care those with positive test results. In spite of the early treatment of disease, however, it is obvious that those who have been screened will continue to die for various reasons. Screening tests do not detect all asymptomatic cardiovascular disease, and medical care is not sufficiently advanced to control all diagnosed conditions. Also, physicians may fail to diagnose some conditions which exist in those with positive tests, and new conditions may arise after screening to remain undetected for some time.

Since persons with positive tests will have more cardiovascular disease than

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those with negative test results we may expect that death rates will also be higher in the positive group Thus, deaths may form a useful basis for evaluating screening tests, since the more effective tests will separate groups with high death rates.

The purpose of this paper therefore, is to present mortality figures for 2,298 residents of Baltimore Maryland who took four screening tests for cardiovascular disease in 1954 to compare death rates in those with positive and those with negative test results and to describe methods for using death figures to evaluate cardiovascular screening tests

Background of this study

In the last three months of 1954 the Commission on Chronic Illness invited 6 967 selected residents of Baltimore who were 17 years of age and older to attend a clinic for multiple screening Those invited were part of a random sample of the city population who on the basis of a household interview some months previously[3] were reported to be free from serious health problems.

Of those invited 2,023 attended for screening An additional 275 persons, who desired to attend after they had read newspaper descriptions of the clinic, took the tests. Of the total number who were screened 35 per cent were under 35 years of age 39 per cent were between 35 and 49 years, and 26 per cent were 50 years and older Seventy-nine per cent of those screened were white persons, and 45 per cent were males.

The follow-up procedures, to determine the status of each person on Dec 31 1959 have been fully described elsewhere[3] By searching city and suburban directories for Baltimore and its surrounding area, we obtained more recent addresses and phone numbers for part of the study group We then mailed a mimeographed letter and questionnaire to each individual 52 per cent of those thus contacted returned the answered questionnaires. For an additional 23 per cent, questionnaire answers were obtained by phone. Finally we searched the 1955-1959 *death certificate files* for the names of all those who were not contacted and to confirm deaths reported in the returned questionnaires.

The follow-up program clarified the current status of 2 031 of those who had been screened Information was incomplete for 267 individuals 12 per cent of all screened we believed that they were not then resident in the Baltimore metropolitan area and knew that they had not died in Maryland in the 5 years after being screened For the purposes of this paper all of this group are assumed to be alive

Tests used in 1954

Of the four cardiovascular tests used at the original clinic in 1954 the first was a questionnaire which included two questions on symptoms for cardiovascular disease (1) Do you ever have distress pain or an uncomfortable feeling in the chest while walking on the street or up inclines or steps (2) While walking are you forced to stop in order to rest The questionnaire test was called positive only when both answers were affirmative

The second test was a 70-mm chest x ray film, which a chest physician read for abnormalities of both lungs and heart.

An electrocardiogram was the third test it consisted of three bipolar and three augmented unipolar limb leads taken while the individual was lying down Each tracing which was annotated with the age and blood pressure of the subject was classified by a cardiologist as normal doubtful or abnormal The revised recommendations of the Framingham Epidemiology Study[4] guided the cardiologist in classifying the tracings In this paper those electrocardiograms which were read as doubtful or abnormal are regarded as positive.

Finally the blood pressure was measured after each individual had been reclining for several minutes. Master Garfield and Walters[5] have suggested that the upper limits of normal pressure increase with age. On the basis of their figures the Baltimore screening levels were 150 90 mm. Hg for persons under 35 years 160 96 mm. Hg for those 35 through 49 years and 170 100 mm Hg for those 50 years or older The test result was regarded as positive if both systolic and diastolic pressures were above those levels, if the systolic pressure alone was 20 mm Hg or more above the screening level or if the dias-

Table I. Number screened (S) in 1954, number dying (D) during 1955-1959, and deaths per 1,000 screened (D per 1,000) for each test result, by age in 1954

Test result	Age (in years)												Age-adjusted† death rate/1,000
	All ages			Under 35			35-49			50 and over			
	S*	D	D per 1,000	S	D	D per 1,000	S	D	D per 1,000	S	D	D per 1,000	
All results	2,298	105	45.7	790	5	6.3	862	20	23.2	631	80	126.8	52.1
Cardiovascular test positive	849	71	83.6	107	2	18.7	333	11	33.0	400	58	145.0	65.6
Cardiovascular test negative	1,449	34	23.5	683	3	4.4	529	9	17.0	231	22	96.2	39.2

*Includes those of unknown age.
†Calculated by the direct method for a population containing equal numbers under 35, 35-49, and 50 and over.

ressure alone was 10 mm. Hg or more bove the screening level.

Death rates by group test results

Table I distributes the 2,298 persons nd 105 known deaths by age when screened nd by the group test result. In each age ange those with positive cardiovascular ests had death rates markedly higher than hose with negative tests. Since persons vith positive tests included the greater proportion of older individuals, we have nade some adjustment for age to describe he over-all mortality experience (foot ote, Table I). The age-adjusted death ate for those with positive cardiovascular ests was 67 per cent greater than for per sons without such results.

The distribution of causes of death dif fered considerably between those with and those without positive cardiovascular tests. Table II shows that 71 of the 105 deaths (68 per cent) occurred in persons with positive results. 41 of the 50 deaths from cardiovascular causes (82 per cent) occurred in that group. Crude death rates for malig nant neoplasms and other causes were higher in those with positive tests because of the greater proportion of older persons in this group.

Death rates for individual tests

Some persons, including a few who died later, did not take all four tests. Because of mechanical failure, for example, some 400 chest x-ray films were unsatisfactory. Those with unsatisfactory test results were omitted from our calculations. Table III shows the number of persons who completed each test, and the number of those who later died, correlated with age and with test result.

For all tests, persons with positive results had higher death rates. This finding was made in all age groups for the chest x-ray film and electrocardiogram. For the questionnaire, those aged 35-49 had similar death rates for positive and negative results, whereas for the blood pressure test no deaths occurred in those persons under 35 who had a positive result. As expected, older persons had the greater mortality whether results were positive or negative.

Indices of effectiveness

In most studies the screening tests have been evaluated by their effectiveness in separating persons with specific diseases. In this study, we desire to evaluate each test by its success in separating those who died in the 5 years after they were screened. Not all deaths were caused by cardiovascular disease, of course. However, if the electrocardiogram, for example, successfully separates persons with noncardiovascular disease as well as those with cardiovascular disease, this analysis gives due credit for this additional yield.

Table IV based on figures in Table III presents five indices which have some value in measuring this performance. *Death Sensitivity* which is the number of deaths classified as positive by the test divided by all deaths, is listed in column *A* Since a test may seem effective by this index, but produce large numbers of false positive results in those who do not die, death sensitivity can be considered only along with the following index. *Death Specificity* is the percentage of all 5-year survivors classified as negative by each test (column *B*) All four tests give satisfactory results when these indices are considered jointly although the blood pressure measurement is the least effective.

Column *C* shows the age-adjusted death rates in persons with positive tests. Here the questionnaire gives the highest value suggesting that this index is an inadequate sole criterion for measuring test performance.

Age-adjusted death rates in persons with negative tests are given in column *D* The lower this death rate the more effective was the test. Ranking high in efficiency are the chest x-ray film and the electrocardiogram. The death rate in persons with negative tests is a criterion which

Table II Number of deaths and crude death rate in persons with positive and with negative cardiovascular tests by cause of death 1955–1959

Cause of death	*Number of deaths*		*Crude death rate 1,000*	
	Cardiovascular test		*Cardiovascular test*	
	Positive	*Negative*	*Positive*	*Negative*
All causes	71	34	83 6	23 5
Hypertensive disease (440-447)	10	3	11 8	2 1
Vascular lesions of central nervous system (330-334)	4	1	4 7	0 7
Other cardiovascular disease (400-434 450-468)	27	5	31 8	3 4
Malignant neoplasms (140-205)	10	12	11 8	8 3
Other causes	20	13	23 5	9 0

Table III Number screened (S) in 1954 number dying (D) during 1955 1959 and deaths per 1 000 screened (D per 1,000) for each screening test by age in years

Test	*Result*	*Age (in years)*											
		All ages			*Under 35*			*35–49*			*50 and over*		
		S	*D*	*D per 1,000*	*S*	*D*	*D per 1,000*	*S*	*D*	*D per 1,000*	*S*	*D*	*D per 1,000*
Chest x-ray film	+	394	49	124 4	60	2	33 3	106	4	37 7	228	43	188 6
	−	1 642	39	23 8	669	3	4 5	665	13	19 5	308	23	74 7
ECG	+	315	51	161 9	42	1	23 8	86	3	34 9	187	47	251 3
	−	1 977	54	27 3	748	4	5 4	775	17	21 9	454	33	72 7
Blood pressure	+	167	25	149 7	13	0	0 0	59	4	67 8	95	21	221 0
	−	2 125	80	37 6	777	5	6 4	802	16	20 0	546	59	108 1
Questionnaire	+	147	24	163 3	14	1	71 4	44	1	22 7	89	22	247 1
	−	2 014	73	36 2	739	3	4 1	766	18	23 5	496	52	104 8

Table IV Indices of effectiveness in screening for deaths during 1955 1959

Test	Death sensitivity* (A)	Death specificity† (B)	Age-adjusted death rates/1,000 Positive (C)	Age-adjusted death rates/1,000 Negative (D)	Age-adjusted mortality ratio‡ (E)	Average ranking (F)
Chest x-ray film	55.7	82.3	86.6	32.9	2.6	3
ECG	48.6	87.9	103.5	33.3	3.1	1
Blood pressure	23.8	93.5	96.3	44.8	2.1	4
Questionnaire	24.7	94.0	113.7	44.1	2.6	2

*$\frac{\text{Deaths classified positive}}{\text{All deaths}} \times 100$

†$\frac{\text{8-year survivors classified negative}}{\text{All 8-year survivors}} \times 100$

‡Death rate in positives/Death rate in negatives.

correlates fairly closely with the joint consideration of sensitivity and specificity

Finally column *E* gives the mortality ratio the death rate in persons with positive tests divided by the death rate in persons with negative tests. Again the electrocardiogram ranks high and the chest x ray film and blood pressure measurement come next.

At present we can say only that each criterion contributes something to the evaluation of the tests none seems to be outstandingly good or bad and none is adequate for sole consideration Therefore we have produced an average ranking for each test (column *F*) giving equal weight to each of the five indices. This average ranking suggests that the electrocardiogram is the most effective of the four tests in separating a high-mortality group the questionnaire and chest x-ray film come next whereas the blood pressure measurement was least effective although still of value

Discussion

To evaluate screening tests the use of diagnoses made as a result of screening has had many faults. In most studies persons with negative tests are not examined to detect false negative results Many of the diagnostic examinations may be inadequate for several reasons The diagnosis of asymptomatic disease is not well taught in medical schools thus, general practitioners face many problems in deciding what labels to attach to asymptomatic patients with positive tests. Some physicians, much impressed by the electrocardiographic abnormality found on screening for example may attach an otherwise unjustified diagnosis of heart disease other physicians, because they resent the screening program or are embarrassed because they *had not previously* detected a positive finding may readily attach a negative label

In contrast to medical diagnoses, deaths are impartial events which depend little on the diagnostic acumen of physicians Since groups with high death rates need medical care more urgently than those with low rates, screening tests perform a useful function if they refer high-mortality groups for medical care. The use of death rates to evaluate the performance of screening tests has therefore some validity

The degree of validity is not perfect however Some noncardiovascular tests aim at conditions which rarely cause death the hemoglobin level for anemias or the intraocular pressure for glaucoma are examples of this group Mortality studies can underevaluate the success of such tests. Also some screening tests, such as the chest x-ray examination for tuberculosis detect conditions for which medical care is highly effective A comparison of death rates between persons with positive and those with negative test results would

again underevaluate the effectiveness of such tests. However the cardiovascular tests are probably treated fairly by mortality data since the conditions detected are frequent causes of death and are only moderately affected by presently available medical treatment

This follow-up study in Baltimore suffers from the defect of incomplete information for 12 per cent of all those who were screened. The 267 incompletely traced persons include more in the younger age groups, more nonwhites and more with negative tests than do those whose current status is accurately known. This defect has probably had little effect on death figures for each test and for the ranking of tests, but may have produced lower death rates in those with negative tests

The second major problem in this study is the relatively small number of persons screened and the small number of deaths analyzed Therefore, age groups had to be broad in this presentation, and even the "age adjusted death rates were rather crude adjustments.

Conclusions and summary

To evaluate the effectiveness of four cardiovascular screening tests this study has used 5-year mortality figures for 2,298 residents of Baltimore who took the tests in 1954. It has shown that such tests separate persons whose death rates are 67 per cent higher than those with negative tests and who can thus be given priority in medical care. This finding gives a sound basis for screening and weakens the contention that physicians must examine all adults at regular intervals not just those with positive tests.

The four tests separated 68 per cent of those who later died and 82 per cent of those who died from cardiovascular causes. We have presented five indices which use death rates to evaluate screening tests. Each index has good and bad points, and no one index is adequate to form the sole basis for evaluation The indices suggested that all four tests gave adequate performance In order of decreasing effectiveness the tests were electrocardiogram questionnaire chest x-ray film and blood pressure measurement.

Little is known of how much persons with positive cardiovascular tests benefit by the early detection of their diseases Such testing may fail in its ultimate aim to reduce illness disability and death in the population if medical care does not control the diagnosed conditions. Only when additional research has clearly established the benefits of early detection can screening programs be encouraged widely in the United States.

I should like to acknowledge the significant contribution of Miss Rose Mary Jacobs, M.A., and Mrs. Janet Haro to this study

REFERENCES

1 National Office of Vital Statistics Monthly Vital Statistics Report. Annual Summary for 1959—Part 2 8:28 1960
2. Commission on Chronic Illness Chronic illness in a large city Cambridge, Mass 1957 Harvard University Press.
3 Wylie, C M Participation in a multiple screening clinic, with five-year follow-up Public Health Rep 76:596 1961
4. Kurlander A B Hill, E. H., and Enterline, P E An evaluation of some commonly used screening tests for heart disease and hypertension, J Chron. Dis 2:427 1955
5 Master A. M Garfield A M and Walters, M B Normal blood pressure and hypertension new definitions, Philadelphia, 1952 Lea & Febiger

Time expansion in vectorcardiography
The advantages of magnetic tape recording

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The vectorcardiogram, which simultaneously displays the voltages recorded along two perpendicular axes in a proper angular and phase relationship, has been recognized as an important additional means of analyzing the electrical events of the cardiac cycle. There are limitations of this recording technique. One of the most important of these is the flare spot at the center of the screen which results from (a) the superimposition of P, QRS, and T loops and (b) the base line interval between these events. This flare spot often obscures the initial and terminal forces of the ventricular complex, which may be of considerable diagnostic importance though of small magnitude.

Many techniques have been used to circumvent the afore-mentioned difficulty. Mann's monocardiograph[1] was an early attempt to solve the problem. This technique separated the initial and terminal events by inscribing the loop on slowly moving film, but produced distortion of the body of the loop. Electronic blanking-unblanking circuits have also been proposed.[2,3] These utilize an event of the cardiac cycle, usually the P or QRS complex, to actuate a series of relays which unblank the beam of the cathode ray tube only during a selected portion of the cycle. This eliminates the center flare and the confusion caused by multiple crossing of P, QRS, and T loops. Such circuits are dependent on a constant cycle length for the precise dissection of the electrical events and therefore are usually not applicable to irregular rhythms. Also, the normal physiologic variations in cycle length may be sufficient to disturb their proper function. Another method of elimination of the center flare is to attenuate the intensity of the light beam in inverse proportion to the speed of the sweep of the loop.[4]

Even when these devices are used, superimposition of efferent and afferent limbs of the loop is a common occurrence, and visual inspection of the pathway of the beam is often necessary. This can be accomplished by motion pictures of the face of the cathode ray tube, but analysis of loops recorded by this technique is said to be difficult.

This report presents a technique for recording vectorcardiograms which utilizes magnetic tape to slow the inscription of the tracing. This method permits manual

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manipulation of the camera shutter and beam intensity which in turn leads to increased clarity of the initial and terminal forces.

Method

The Frank lead system[3] has been selected for use in this laboratory because of its theoretical advantages and its ease of application. Fifty thousand ohms were used as the unit of resistance

The voltages across the X Y and Z terminals of the Frank resistor network were amplified by Sanborn 350-3,200 pre amplifiers. The outputs of these preamplifiers were attenuated if necessary to prevent distortion due to overloading of the tape recorder at later stages.

The outputs of the three preamplifiers were recorded simultaneously on three separate channels of an Ampex FR 100A FM magnetic tape recorder-reproducer The input and output of each channel were monitored during the recording by means of a Tektronix Type 502 dual beam oscilloscope The recordings were made at a tape speed of 60 inches per second (i.p.s.) At this speed, the frequency response of the magnetic tape system is flat from 0 to 10 000 cycles per second (c.p.s.) ± 1 to 2 decibels and the interchannel time displacement error is less than 10 μsec between tracks.

After the recording of a number of cardiac cycles, the tape was played back at a speed of 1 7/8 i.p.s. (time expansion factor 32) The frequency response of the system at this speed is flat from 0 to 312 c.p.s. (equivalent to 0 to 9 984 c p.s. at the original speed)

From the recorded voltages X Y and Z the appropriate pairs were selected from the reproduction channels and displayed on the oscilloscope as the frontal, horizontal and right sagittal plane loops. The intensity of the cathode-ray beam was modulated repetitively which produced interruptions of the displayed loop for timing purposes A Grass square wave stimulator (Model S4B) was used for this purpose. The beam was modulated at a frequency of 15 6 times per second which corresponds to a frequency of 500 interruptions per second at the original speed of the loop. The loops were photographed with a Hewlett Packard oscilloscope camera, using 3 000 speed Type 47 Polaroid film The camera shutter was opened and closed manually to record the desired portion of the cycle Intensity of the beam was also modulated by the operator to avoid overexposure during recordings of the T and P loops Interrupted and uninterrupted loops in each of the three planes were photographed

Scalar tracings of the X Y and Z voltages were recorded either directly from the preamplifiers or from the taped records at a speed of 60 i.p.s. The recordings were made on a Consolidated Engineering Recording Oscillograph (Model 5-116) at a paper speed of 1 or 2 i p.s.

Discussion

The chief advantage of recording physiologic events on magnetic tape is that of flexibility of presentation of the stored data. The analogue data can be reproduced as scalar tracings at a variety of speeds and can also be converted into digital form In either form the data can be analyzed automatically by computers or stored for future recovery [4] The feature utilized in the method under discussion is that of time-base expansion and contraction, which is accomplished by recording at one tape speed and reproducing at a different tape speed

Because of the comparatively low frequencies involved in the electrocardiogram



Fig. 1 *Left* QRS and T loops recorded without time expansion. *Right* QRS from the same subject, recorded by technique described.

and other physiologic data special means must be used for recording such events on magnetic tape. The Ampex FR 100A system utilizes the voltage from the preamplifier to modulate a carrier frequency which in turn is recorded on the magnetic tape. This modulated carrier frequency is then demodulated in order to recover the original voltage. Such a system is capable of recording frequencies down to zero cycles per second. The upper frequency which can be accurately recorded varies with the speed of the tape. The frequency response of the entire system is limited by the preamplifiers rather than by the tape recorder-reproducer.

A thirty-two-fold time expansion is achieved by recording at 60 i.p.s. and reproducing at 1 7/8 i.p.s. The degree of slowing possible with other equipment can be determined by the ratio of the highest recording speed to the lowest reproducing speed.

As a result of this time expansion, the frequency of physiologic events is reduced by a factor of 32. Thus, a wave of 100 c.p.s. is reproduced at approximately 3 c.p.s. For this reason, devices which have a lower frequency response than the oscilloscope, such as direct writing X-Y plotters, can be used for recording.

By means of the system described, satisfactory loops with clear definition of initial and terminal QRS forces are usually obtained on the first attempt. If the events of a given loop deserve more detailed analysis, the loop can be photographed at a greater amplification.

In this laboratory, loops are analyzed directly from the photographs and from loops redrawn to scale on graph paper. This is probably the optimal technique for the usual clinical purposes of the vectorcardiogram. For certain types of research, however, analysis can be done directly from the tape by electronic computers. This is usually accomplished by prior conversion of the data from analogue to digital form.

Summary

A method of recording vectorcardiograms which utilizes magnetic tape to obtain time expansion is described in this report. This method makes it possible to open and close the camera shutter and to modulate the intensity of the beam manually. Manual control under direct vision avoids the problem of center flare and leads to increased clarity of the loop. Time expansion also allows one to use recording devices which have a lower frequency response than the cathode-ray tube. The flexibility of handling the recorded data is an additional advantage.

REFERENCES

1. Mann, H.: Monocardiography: a method of analyzing the electrocardiogram, AM. HEART J. 15:681, 1938.
2. Hellerstein, H. K., Shaw, D., and Sano, T.: Dissection of the vectorcardiogram: differential vectorcardiography, AM. HEART J. 47:887, 1954.
3. Briller, S. A., Marchand, N., and Kossmann, C. E.: A differential vectorcardiograph, Rev. Scientific Instrument 21:805, 1950.
4. Mizao, T., Kimura, N., and Yoshida, T.: Research on vectorcardiography. Report 22. Research especially on the method of inscription, Nippon J. Angiocardiol. 13:118, 1949. Quoted by Hellerstein et al.
5. Frank, E.: An accurate, clinically practical system for spatial vectorcardiography, Circulation 13:737, 1956.
6. Pipberger, H. V., Freis, E. D., Taback, L., and Mason, H. L.: Preparation of electrocardiographic data for analysis by digital electronic computer, Circulation 21:413, 1960.

Response of phonocardiographic and hemodynamic features of mitral stenosis to inhalation of amyl nitrite

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Accentuation of the diastolic murmur of mitral stenosis during inhalation of amyl nitrite was described by Morison [1] and this observation has been subsequently confirmed.[2,3] In the present study the response of the auscultatory and phonocardiographic features of mitral stenosis to inhalation of amyl nitrite was investigated further and supplemented by information on the changes in intracardiac pressures.

Method

Twenty-six patients with pure or dominant mitral stenosis were investigated. Information as to the dimensions of the orifice and the gross pathologic condition of the valve was available for 13 patients who underwent valvotomy during the period of the study.

The phonocardiograms were recorded from the left lower sternal border and the mitral area before the patients inhaled amyl nitrite for 15 seconds, immediately after inhalation, and then every 15 seconds for 2 minutes. In 8 patients, amyl nitrite was given during catheterization of the right side of the heart. The changes in systemic pressure (8 patients), pulmonary wedged pressure (8 patients), pulmonary arterial pressure (6 patients), and arteriovenous oxygen difference (4 patients) were recorded. Because of the rapidly changing levels it was not possible to obtain meaningful measurements of oxygen consumption.

Observations were also made on the R-1 and A_2-OS phonocardiographic intervals. The former was determined as the time between the R wave of the electrocardiogram and the loudest component of the first sound at least 0.02 second after its onset, since the initial vibrations in patients with mitral stenosis are due to closure of the tricuspid valve.[4] The A_2-OS interval was measured from the sound of aortic closure to the opening snap. In order to study the effect of amyl nitrite independently of the changes produced by tachycardia, the duration of these intervals before and after the inhalation of amyl nitrite was compared in cycles preceded by similar diastolic intervals. This was possible in most patients since there was appreciable variation in the cycle length due to auricular fibrillation.

Results

During the inhalation and for 1 minute thereafter the patients complained of throbbing in the head, dizziness and headache, and were tachypneic and flushed. Inversion of the T wave occurred in the electrocardiogram of one patient (Fig. 1) without attending precordial discomfort.

The systemic pressure fell immediately and reached its lowest level in 15 to 30

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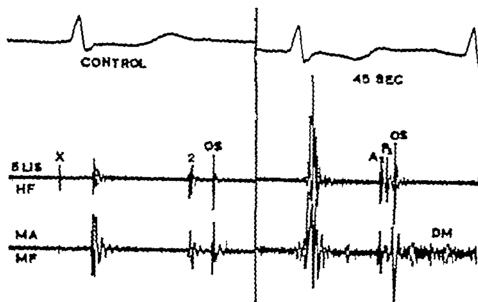


Fig. 1 Accentuation of indistinct diastolic murmur and abbreviation of A_2-OS interval from 0.08 to 0.04 sec. Increased amplitude of first sound and of opening snap (*OS*). *X* Artifact. Note inversion of T wave. Time between vertical lines equals 0.04 sec.

onds (this and all other times indicate points from the start of the inhalation) tachycardia ensued and the blood pressure returned to control levels in 90 to 120 seconds. Narrowing of the arteriovenous oxygen difference was observed during the latter stage (Table I). This probably implies coincident increase in cardiac output since diminution of oxygen consumption seems unlikely in view of the tachypnea and flushing. The mean pulmonary wedged pressure increased in 30 seconds and for approximately 1 minute (Table I). The pulmonary arterial pressure was not modified initially and was slightly elevated between 30 and 90 seconds.

Significant accentuation of the apical diastolic murmurs was observed (Figs. 1 and 2) with the exception of 2 patients who had pulmonary hypertension and vascular resistance of 15 and 17 units. An apical systolic murmur was present in 3 patients: it became fainter in 2 patients which suggested that it was due to mitral insufficiency[3] and was accentuated in the third which suggested the presence of aortic stenosis.[3]

Accentuation of the first sound was noted in 12 patients during the period of tachycardia. In addition to the provisions made in the section on method coincident accentuation of the opening snap ensured that the sound represented mitral closure. Five patients of this group underwent valvotomy: supple leaflets were found in 3 patients and a moderate degree of rigidity and calcification was noted in the other 2. Of the remainder in whom no appreciable change in the amplitude of the first sound and the opening snap occurred 8 underwent operation. Considerable rigidity and calcification was found in all of them. In both groups the area of the valve as estimated at the time of operation was of the same range (0.8 to 1.4 square centimeters).

The aortic component of the second sound became faint during systemic hypotension whereas the pulmonary component was not affected. Significant abbreviation of the A_2-OS interval was noted 15 seconds after the inhalation and further abbreviation in 30 seconds (Figs. 1, 2, and 3). The R_1 interval was usually prolonged in 30 seconds (Fig. 3).

Discussion

The effects of amyl nitrite appear to be related to the two phases of its action, i.e. the initial prompt fall of systemic pressure and a subsequent increase of cardiac out

Fig. 2 Accentuation of previously inaudible diastolic and presystolic murmurs. Carotid sphygmogram shows changes of systemic pressure in a qualitative fashion. A_2–OS interval was progressively shortened so that OS merged with A_2 at 45 sec. tachycardia and shorter cycle length cannot have been responsible alone for striking abbreviation of A_2–OS interval. Marked accentuation of first sound and opening snap is also seen.

put. Higher output and abbreviation of diastole due to the tachycardia most likely produced the rise in pulmonary wedged pressure. The small elevation of pulmonary arterial pressure was probably secondary to the rise in wedged pressure. The absence of a drop in pulmonary arterial pressure during the stage of systemic hypotension at a time when pulmonary flow was, as yet unchanged or even low suggests that amyl nitrite did not act as a vasodilator on the lungs of these patients. That this may be generally true is suggested by similar findings in a large series of patients with congenital heart disease. this series contained patients with both normal and elevated pulmonary arterial pressure.[4]

The reported accentuation of mitral

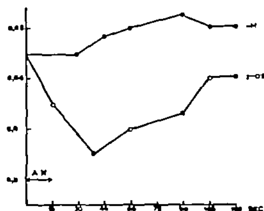


Fig. 3 Effect of amyl nitrite upon duration of R–M and A_2–OS intervals, corrected for rate, in a representative case. Ordinat : Duration of the intervals in hundredths of a second. Abscissa: Seconds after the inhalation, which is shown by the line A–N

Table I Hemodynamic effects of inhalation of amyl nitrite

Case number	Sex age		Systemic arterial pressure	Pulmonary arterial pressure	Pulmonary wedged pressure (mean)	Arteriovenous oxygen difference (%)
1	F 46	C	104/63	42/20	26	35
		AN	84/60	48/22	33	27
2	F 30	C	109/62		15	
		AN	56/42		25	
3	F 32	C	137/68	62/27	24	34
		AN	80/47	66/29	35	34
4	F 44	C	114/72	40/18	16	38
		AN	88/54	45/21	22	30
5	F 48	C	146/86		40	
		AN	122/62		48	
6	F 51	C	142/87	35/17	20	23
		AN	105/59	39/20	29	19
7	F 39	C	124/78	90/40	35	
		AN	89/53	94/42	43	
8	F 42	C	155/89	159/72		
		AN	112/61	164/74		

*C Control observation AN Under the influence of amyl nitrite.
The lowest level of systemic pressure recorded is indicated, whereas the effect on the other three parameters is shown during the stage of return of systemic pressure to control levels. All pressures are expressed in millimeters of mercury from the mid thoracic level.

stolic murmur[1-3] was further confirmed and in our hands the procedure appeared to be a more effective means than exercise or turning to the left lateral decubitus position to make subthreshold mitral stenotic murmurs apparent. Failure of the diastolic murmur to become louder in 2 patients with severe pulmonary hypertension may not be unusual in such patients because they often have low relatively fixed cardiac output. These exceptions suggest that the test is more reliable in the case of positive results whereas negative results do not allow exclusion of mitral stenosis. Another advantage of the inhalation of amyl nitrite is the information which it may give in regard to the origin of an accompanying apical systolic murmur[3] as was mentioned in 3 such cases in this series.

It has been reported that the intensity of the first sound does not change with varying cycle length in patients with mitral stenosis,[7] particularly when the stenosis is tight.[4] The few observations presented here would suggest that it is the degree of pathologic deformity rather than the severity of obstruction which determines whether the first sound is intensified during tachycardia which develops after inhalation of amyl nitrite.

Abbreviation of the A_2-OS interval during inhalation of amyl nitrite was originally observed by Margolies and Wolferth,[4] who ascribed it to the tachycardia and the correspondingly shorter cycles. It was observed in our cases, however, that abbreviation occurred although the influence of rate had been eliminated. The A_2-OS interval represents the time taken by left ventricular pressure to fall from the level of the aortic incisura to the crossover with the left atrial pressure. The fall in systemic pressure and the rise in left atrial pressure as a result of the administration of amyl nitrite bring these points toward each other and thereby produce abbreviation of the interval irrespective of any changes due to variation in cycle length. The rise in left atrial pressure was also probably responsible for the prolongation of the R-1 interval, since it would thus take longer for the ascending limb of the left ventricular pressure curve to exceed left atrial pressure and close the mitral valve.

Summary

The effects of the inhalation of amyl nitrite were studied in 26 patients with mitral stenosis. An initial drop in systemic pressure was observed, but it was not accompanied by a fall in pulmonary arte

ral pressure. This was followed by increases in cardiac output and in pulmonary wedged pressure and by a slight rise in pulmonary arterial pressure. Accentuation of mitral diastolic murmurs occurred and the test thus proved to be useful for the diagnosis in cases of mitral stenosis with faint or inaudible murmurs. Increased intensity of the first sound during tachycardia which occurred after inhalation of amyl nitrite was seen in those patients who were found at operation to have valves which were not severely malformed. Abbreviation of the A–OS interval and prolongation of the R 1 interval were shown to be due to the hemodynamic changes produced by the drug, independently and in addition to its effect on the heart rate.

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REFERENCES

1. Morison, R. A. The value of amyl nitrite in the diagnosis of mitral stenosis, Brit. M. J. 1:452, 1918.
2. Levine, S. A., and Harvey, W. P. Clinical auscultation of the heart, Philadelphia, 1949, W. B. Saunders Company.
3. Vogelpoel, L., Nellen, M., Swanepoel, A., and Schrire, V. Use of amyl nitrite in the diagnosis of systolic murmurs, Lancet 2:810, 1959.
4. Hultgren, H., and Leo, T. Phonocardiographic features of combined mitral stenosis and insufficiency, Medicine 38:103, 1959.
5. Barlow, J., and Shillingford, J. The use of amyl nitrite in differentiating mitral and aortic systolic murmurs, Brit. Heart J. 20:105, 1955.
6. Bourouros, G. A., and Lessof, M. H. The inhalation of amyl nitrite: a useful test in the assessment of heart murmurs and in the hemodynamic diagnosis of heart disease. (In preparation.)
7. Rytand, D. A. The variable loudness of the first heart sound in auricular fibrillation, Am. Heart J. 37:187, 1949.
8. Margolies, A., and Wolferth, C. C. Opening snap ("claquement d'ouverture de la mitrale") in mitral stenosis: its characteristics, mechanism of production, and diagnostic importance, Am. Heart J. 7:443, 1932.

Circulatory responses to hyperventilation and exercise in normal subjects

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Hemodynamic studies during hyperventilation[1-7] have shown varying changes of the cardiac output. Comparison of data from these studies is difficult because of differences in respiratory rate minute volume and position In general however more vigorous voluntary hyperventilation with room air is associated with a rise in cardiac output This increase in cardiac output has been considered to be the result of the muscular exercise involved in the work of breathing[4] Other workers[7] have suggested that the magnitude of the increased work of ventilation is insufficient to result in such an increased output and postulated that changes in pH may be the dominant factor

In the present study the hemodynamic response to exercise was compared with that to hyperventilation in order to determine whether comparable rises in cardiac output with the two stresses are associated with similar changes in other circulatory parameters. Preliminary studies had shown that atropine modified the circulatory response to hyperventilation presumably because of disruption of autonomic regulatory mechanisms by vagal and possibly ganglionic blockade[8] Because atropine in previous studies did not seem to modify the cardiac output response to exercise, the drug was also used in this study in order to exaggerate if possible differences between the circulatory responses to exercise and hyperventilation

Materials and methods

Fourteen young adult male university students were studied in the recumbent and postabsorptive state They were divided into two groups of 7 students each Group I was studied during leg exercise and Group II during hyperventilation Vital statistics on the subjects are given in Tables I and II A No. 6 or No 7 cardiac catheter was passed from the antecubital fossa to the superior vena cava just proximal to the right atrium for measurement of the mean central venous pressure The base line was established 5 cm posterior to the sternal angle Brachial arterial pressure was monitored using an indwelling No 18 Cournand needle Mean arterial and venous pressures were obtained by electrical integration of at least two respiratory cycles. Heart rate was determined from a continuous electrocardiographic tracing A multichannel photographic oscil

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lographic recording device* was employed for continuous simultaneous measurements. Cardiac output, mean circulation time, and the so-called "central blood volume" were determined by means of the T 1824 dye dilution technique of Hamilton.[8] The dye was injected and rapidly flushed into the superior vena cava, and successive 2-second samples were collected from the brachial artery and allowed to clot. The serum was read at 620 and at 540 mμ to correct for hemolysis. All recorded pressure data were determined immediately before the determination of the cardiac output. Expired air was collected in a Douglas bag in 2 of the hyperventilation studies and in all 7 of the exercise studies, and the oxygen content was determined by means of a Pauling oxygen analyzer to allow estimation of minute oxygen consumption.

Results

1. Group I—Exercise (Tables I and II and Figs. 1-3). Exercising the lower extremities resulted in an increase over the control values in heart rate (69 per cent), cardiac output (105 per cent), stroke volume (18 per cent), central blood volume (42 per cent), and systolic and mean arterial pressures (17 and 20 per cent, respectively; $p < 0.025$). There was no change in mean central venous pressure or in diastolic arterial pressure. The total peripheral resistance decreased 42 per cent. Oxygen consumption increased from 283 ± 36 to 1,033 ± 197 ml./min. and the respiratory minute volume rose from 7.98 ± 3.84 to 22.51 ± 6.93 L./min.

After recovery, atropinization alone resulted in a tachycardia comparable to that achieved during exercise. As in a previous study in this laboratory, atropine produced an increase in cardiac output of only 39 per cent over the control value despite the rise in heart rate of 85 per cent. The stroke volume therefore decreased (−26 per cent). There was a decrease in mean central venous pressure of −4.2 mm. Hg. The total peripheral resistance also decreased, although not so much as with exercise. The central blood volume (Table III) and the arterial pressures (systolic, diastolic, and mean) were unchanged by atropinization. Oxygen consumption showed a slight rise over the control resting value (control value, 283 ± 36 ml./min.; atropine value, 332 ± 39 ml./min.; $p < 0.025$).

When the exercise was repeated after atropinization, a further increase in heart rate ensued (after atropine, 120/min.; exercising after atropine, 141/min.). The cardiac output rose to a level quite comparable to that achieved during exercise before atropinization (before atropine, 12.39 ± 2.55 L./min.; after atropine, 11.94 ± 2.38 L./min.). The stroke volume rose from 73 ± 23 ml./beat to 86 ± 21 ml./beat ($p < 0.05$), but the latter value was still below the unatropinized resting value of 98 ± 20 ml./beat (and much lower than the unatropinized exercising value of 115 ± 31 ml./beat). Central blood volume was significantly increased ($p < 0.025$) but to a lesser degree than prior to atropine. Systolic and mean arterial pressures showed a slight increase with exercise ($p < 0.05$) but less than that observed before atropinization. Mean central venous pressure and diastolic blood pressure were not changed. The total peripheral resistance and oxygen consumption assumed values identical to those with exercise before atropine.

2. Group II—Hyperventilation (Tables II and III and Figs. 1-3). In the second group of 7 subjects, voluntary hyperventilation at 40 respirations per minute brought about increases in heart rate and cardiac output of 69 and 88 per cent, respectively, over control values. These values were very similar to those obtained in Group I with leg exercise. Similarly, the average value for the stroke volume rose slightly with hyperventilation, although in this instance the difference was not statistically significant. In contrast to the observations in Group I, the calculated central blood volume did *not* change with hyperventilation (Table III). Also in contrast to Group I, the arterial systolic pressure did not rise with hyperventilation, but rather showed a slight fall ($p < 0.025$). The mean values for diastolic and mean arterial pressure also showed a slight, but statistically insignificant, decrease. (Transient falls in arterial pressure have been noted with the onset of hyperventilation in previous studies.[3,5,6]) Also in contrast to the exercise study, hyperventilation caused a fall

*Manufactured by Electronics for Medicine, White Plains, N. Y.

Table I. Circulatory changes during exercise before and after atropine in 7 recumbent subjects

Subject	Age (yr.)	Weight (Kg.)	Height (cm.)	State*	Heart rate (beats/min.)		Arterial blood pressure (mm. Hg)					
							Systolic		Diastolic		Mean	
					R†	E†	R	E	R	E	R	E
J.B.$_1$	21	86	176	C	60	115	113	129	63	71	82	102
				A	118	149	118	—	74	—	90	102
J.B.	21	86	176	C	68	106	117	134	64	73	83	99
				A	132	142	115	131	73	69	90	93
E.C.	28	66	175	C	59	102	120	—	62	—	84	—
				A	111	135	—	160	—	88	—	105
P.W.	19	63	178	C	58	103	125	152	85	88	95	112
				A	113	140	113	122	64	63	82	90
E.J.	22	100	184	C	56	110	122	159	72	94	88	115
				A	107	134	123	144	80	82	94	107
C.S.	18	107	189	C	48	96	150	154	93	62	107	107
				A	102	118	148	149	78	72	99	107
L.‡	24	58	170	C	105	131	132	152	77	86	94	110
				A	157	169	126	126	79	74	100	95
Mean	21.8	81.1	178.3	C	64.8	109.3	125.5	146.7	73.7	79.0	90.4	107.5
±S.D.	3.3	19.1	6.3		18.7	11.3	12.3	12.1	19.7	12.1	9.0	6.1
Mean				A	120.0	141.0	124.2	138.7	74.7	75.0	92.5	99.8
±S.D.					18.9	15.6	12.5	14.7	5.9	8.5	6.7	7.1

*C, Control; A, Atropinized.
†R, Resting; E, Exercising.
‡Male patient with possible peptic ulcer.

mean central venous pressure of 3.2 ± 2.3 mm. Hg. The peripheral resistance fell considerably, as it did with exercise. Unfortunately, the oxygen consumption with hyperventilation was only measured in 2 of the 7 subjects. In both it was about twice the resting value, as compared to the almost fourfold increase demonstrated in the exercise study (Group I). In the same 2 subjects the respiratory minute volume increased from 4.97 and 6.43 to 54.81 and 31.98 L./min., respectively.

Atropinization alone in these 7 subjects resulted in changes in all parameters which were in no way different from those enumerated above for Group I (see Table II).

Hyperventilation after atropine resulted in a further increase in rate to 140 ± 18/min., a level identical to that reached with leg exercise after atropinization. In marked contrast to the exercise situation, however, the cardiac output (see Fig. 3) showed no significant rise with hyperventilation over the atropinized control value (atropine alone, 8.68 ± 2.60 L./min.; atropine plus hyperventilation, 9.18 ± 1.46 L./min.). The cardiac output during hyperventilation in the atropinized subject was actually less than during hyperventilation in the unatropinized subject (atropine plus hyperventilation, 9.18 ± 1.46 L./min.; hyperventilation alone, 12.16 ± 1.47 L./min.; $p < 0.01$). The average value for stroke volume was lower with hyperventilation, but this difference (atropine alone, 74 ± 20 ml./beat; atropine

Central venous pressure (mm. Hg)		*Cardiac output (L./min.)*		*Stroke volume (ml./beat)*		*Peripheral resistance (dynes-sec.-cm.⁻⁵)*		*Respiratory minute volume (L./min.)*		*Oxygen consumption (ml./min.)*	
R	*E*	*R*	*E*	*R*	*E*	*R*	*E*	*R*	*E*	*R*	*E*
4 7	6 8	6 54	14 73	109	128	1 000	550	5 96	24 66	352	1 302
1 5	4 0	9 46	14 62	80	98	760	560	6 57	30 35	308	1 [illegible]
6 4	6 0	6 14	12 13	90	114	1 080	650	6 57	19 34	278	944
5 0	5 0	7 55	11 34	57	80	950	660	8 81	19 60	331	98
6 1	—	5 85	9 68	99	95	1 150	—	3 82	16 40	251	774
—	2 3	7 80	10 70	70	79	—	780	6 90	—	267	—
4 3	6 2	6 63	13 59	114	129	1 140	660	7 06	25 56	292	1 063
0 4	2 7	9 32	14 02	84	100	690	510	8 08	20 32	369	916
4 0	3 6	5 49	10 79	98	95	1 280	850	16 62	36 02	327	1 248
1 4	2 8	8 61	8 05	80	61	870	1 060	8 28	33 83	321	1 238
6 0	3 0	5 54	16 20	115	169	1 540	530	7 08	17 45	334	1 061
−1 0	−1 0	10 82	14 00	106	119	730	610	8 56	15 44	384	1 034
−0 5	−0 3	6 10	9 62	58	73	1 230	920	6 72	18 17	247	842
−5 9	−8 0	5 04	10 82	32	64	1 590	700	10 44	22 66	328	816
4 4	4 4	6 04	12 39	97 6	115 1	1 200	690	7 98	22 51	283	1 013
2 4	2 4	0 45	2 55	19 7	30 9	180	160	3 84	6 93	36	197
0 2	1 1	8 40	11 94	72 7	85 8	930	340	8 23	23 70	332	1 088
3 6	4 4	1 86	2 38	23 3	20 9	700	180	1 07	7 00	39	261

and hyperventilation 66 ± 7 ml./beat) does not represent a significant change. Central blood volume did not change with hyperventilation (*Table II*). The systolic arterial pressure with hyperventilation and atropine fell to a significantly lower level than it had done with hyperventilation before atropine. In this instance there was also an impressive fall in the diastolic and mean pressure in one subject (G.T.) the arterial pressure fell to a frankly hypotensive level. The mean venous pressure already significantly lowered by atropine showed a trend toward a slight additional fall with hyperventilation but this difference was not statistically significant. The calculated peripheral resistance did not fall as much as it had done before atropine. In the 2 subjects in whom it was measured the oxygen consumption during hyperventilation was the same as during hyperventilation without atropine.

Discussion

Grollman in 1930[1] and Proger in 1933[2] stated that, when the cardiac output increases during hyperventilation, the rise must be the result of the muscular exercise involved in breathing. Since then much has been said about the work of breathing but the circulatory consequences are still not clear. Studies in this laboratory[4,6] have demonstrated impressive increases in cardiac output during vigorous voluntary hyperventilation. Richardson and co-workers reported that both infusion

Table II Circulatory changes during hyperventilation before and after atropine in 7 recumbent

Subject	Age (yr)	Weight (Kg)	Height (cm)	State*	Heart rate (beats/min)		Arterial blood pressure (mm Hg)					
							Systolic		Diastolic		Mean	
					R†	H†	R	H	R	H	R	H
G.T	23	84	185	C	54	102	154	145	62	64	86	85
				A	120	150	171	113	90	58	115	66
P W	19	62	178	C	64	126	127	126	59	51	73	72
				A	90	132	117	107	57	44	75	67
C.F	23	90	188	C	78	—	—	—	—	—	—	—
				A	114	150	—	—	—	—	—	—
R.F	21	74	188	C	60	120	114	108	63	55	76	76
				A	108	120	110	115	66	64	78	75
P.F	20	83	180	C	60	102	124	109	70	59	86	77
				A	114	138	109	—	72	—	84	—
R.	21	78	174	C	65	112	135	130	70	57	91	83
				A	145	169	160	100	84	46	116	71
McL.	21	70	183	C	75	97	128	126	68	66	85	76
				A	120	118	140	118	84	63	108	85
Mean	21 1	77 3	182 3	C	65 1	109 8	130 3	124 0	65 3	59 7	82 8	78 2
±S.D	1 3	9 5	12 9		8 6	11 5	13 5	13 9	4 6	5 6	6 8	4 9
Mean				A	115 8	139 6	134 5	110 6	76 2	55 0	96 0	72 8
±S D					16 4	18 2	26 7	7 2	13 3	9 4	19 0	7 7

*C Control A Atropinized
†R Resting H Hyperventilating

of bicarbonate and hyperventilation with room air caused increases in cardiac output However when vigorous hyperventilation was performed with the addition of quantities of carbon dioxide to the inspired air sufficient to prevent a pH change no significant increase in cardiac output was noted Hyperventilation on 5 per cent carbon dioxide in this laboratory[4] has resulted in a mean increase in cardiac output of 43 per cent Changes in pH were not monitored in this study however

In the present study the finding of very similar rises in both heart rate and cardiac output in two groups of individuals during leg exercise and hyperventilation led to the question whether the increases in cardiac output in both instances were due to a similar mechanism i.e. muscular exercise Careful comparison of changes in various hemodynamic parameters in the two situations revealed several qualitative and quantitative differences between exercise and hyperventilation The arterial pressure which rose with exercise showed a tendency to fall with hyperventilation The central venous pressure was unchanged during exercise but fell during hyperventilation The calculated central blood volume rose with exercise but showed no significant change in the hyperventilation study The response of cardiac output to the two maneuvers in atropinized subjects was quite different a considerable increase occurred with exercise but there was no significant increase with hyperventilation

subjects

Central venous pressure (mm Hg)		*Cardiac output* (L./min.)		*Stroke volume* (ml./beat)		*Peripheral resistance* (dynes sec -cm⁻⁵)		*Respiratory minute volume* (L./min.)		*Oxygen consumption* (ml./min.)	
R	H	R	H	R	H	R	H	R	H	R	H
0	−3	7 18	13 13	133	129	960	520	—	—	—	—
−4	−2	13 45	11 89	112	79	690	440	—	—	—	—
0	−1	6 93	12 25	108	98	840	470	—	—	—	—
−1	−3	7 33	9 24	81	70	820	580	—	—	—	—
—	—	7 44	—	95	—	—	—	—	—	—	—
—	—	7 38	8 78	62	59	—	—	—	—	—	—
−1	−4	4 75	13 68	79	114	1 280	440	—	—	—	—
−3	−6	6 74	7 88	62	66	930	760	—	—	—	—
—	−2	5 71	10 40	95	102	1 200	590	—	—	—	—
—	—	5 96	8 96	52	65	1 130	—	—	—	—	—
+5	−2	5 94	13 17	91	118	1 220	500	4 97	54 81	290	555
−3	−4	10 16	10 02	70	59	910	560	5 21	59 09	302	586
+7	+5	7 35	10 30	98	106	920	590	6 43	31 98	338	487
+1	−1	9 71	7 50	81	64	890	900	3 95	25 48	262	415
+2 2	−1 2	6 47	12 16	99 8	111 2	1 070	520	5 69	43 39	314	521
3 6	3 2	1 02	1 47	17 0	11 5	180	60	—	—	—	—
−2 0	−3 2	8 68	9 18	74 3	65 7	890	650	4 58	42 29	282	500
2 0	1 9	2 60	1 46	66 0	6 9	140	180	—	—	—	—

Differing responses in arterial pressure, central venous pressure, calculated central blood volume and cardiac output after atropine all make it likely that the increases in cardiac output which are seen in normal subjects with the two maneuvers result from differing circulatory mechanisms.

The problem of the measured changes in central blood volume with exercise has been discussed in detail by Braunwald and Kelly.[11] All investigators[11, 4] have agreed that the calculated central blood volume which is derived from samples of brachial arterial blood is increased by leg exercise. There is no agreement as to the mechanism which causes the rise in the calculated value but Gleason and associates[10] and Marshall and co-workers[11] have demonstrated that changes in the pattern of arterial flow may produce large changes in this calculated value in the absence of any change in the actual volume of blood in the heart, and lungs. It would seem that great caution should be used in attaching any significance to changes of this parameter during stresses which are known to produce changes in the pattern of arterial flow

In the present study there was no significant mean rise in central blood volume with hyperventilation in contrast to the situation with leg exercise. In 1958 Gleason and co-workers[9] suggested that an increase in the central blood reservoir might occur with hyperventilation but their data do not show any increase in calculated

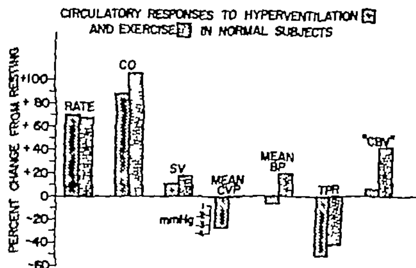


Fig. 1. See text.

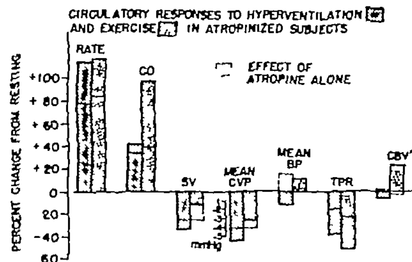


Fig. 2. See text.

tral blood volume.* There seems to be no doubt that with hyperventilation there is active venoconstriction in the peripheral veins which may propel the blood centrally.[illegible] Eckstein and associates[illegible] showed an increase in *transmural* central venous pressure which would be consistent with *an increased amount of blood* within the central reservoir.

The data in the study do not completely elucidate the mechanisms whereby the cardiac output is increased either in leg exercise or in vigorous voluntary hyperventilation. They do suggest that the view commonly held that the increase in cardiac output with voluntary hyperventilation must be caused by the exercise of the respiratory muscles in breathing may be incorrect. The study lends support to the view expressed by Richardson and associates[7] that the thoracic blood pump is of doubtful importance in hyperventilation.

Of particular interest is the observation that hyperventilation in the unatropinized subjects resulted in a cardiac output of 12.16 ± 1.47 L./min. whereas hyperventilation in the atropinized subjects resulted in a cardiac output of 9.18 ± 1.46 L./min. This difference in response is

*This finding would also be consistent with an increase in tone of the walls of the great veins and cardiac chambers in the chest, without the requirement of an increased volume of blood in the venous system.

Table III Central blood volume with exercise and hyperventilation before and after atropine (L./min.)*

Subject	Before atropine		After atropine		Subject	Before atropine		After atropine	
	Rest	Exercise	Rest	Exercise		Rest	Hyperventilation	Rest	Hyperventilation
J.B.-1	1 93	2 90	1 74	2 44	G T	2 62	2 43	2 78	2 34
J.B.	1 60	2 42	1 45	2 04	P W.-1	2 41	1 66	1 91	2 10
E.C.	1 51	2 20	1 65	2 03	C.F	2 16	—	1 87	1 74
P W 2	1 98	2 68	1 92	2 53	R.F	1 96	2 48	1 89	1 60
E.J	1 70	1 63	1 90	1 44	P.F	2 18	1 89	1 69	1 66
C.S.	2 18	3 84	2 11	2 73	D R.	1 62	2 65	2 32	2 42
J.H	1 20	1 52	1 08	1 71	W McL.	1 89	2 16	2 56	2 36
Mean	1 72	2 45	1 69	2 13	Mean	2 12	2 21	2 14	2 03
±S.D	0 33	0 80	0 34	0 46	±S.D	0 33	0 38	0 41	0 34
Δ		+0 73		+0 44	Δ		+0 09		−0 11
P		<0 025		<0 05	P		>0 5		>0 2

*Dye injected into the superior vena cava and sampled from the brachial artery

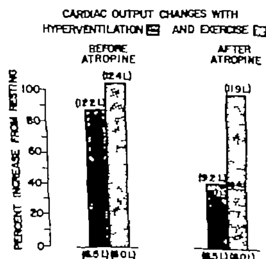


Fig 3 See text.

highly significant ($p < 0.01$) The reason for this difference is not apparent

Summary and conclusions

1 In an attempt to elucidate the genesis of the increased cardiac output during vigorous hyperventilation two groups of 7 recumbent subjects were studied during leg exercise and voluntary hyperventilation respectively using standard hemodynamic techniques. The subjects were studied again after they had ... atropinized in order to exaggerate if possible, any observed differences

2. Although both groups developed closely comparable increases in heart rate and cardiac output, qualitative differences were found in the responses of mean central venous pressure, the arterial blood pressure the so-called central blood volume and the cardiac output after atropinization.

3 These differences suggest that the rises in cardiac output with muscular exercise and with vigorous hyperventilation may be brought about by different mechanisms.

4 Of particular interest is the observation that the expected rise in cardiac output due to hyperventilation can be blocked by atropine.

REFERENCES

1 Grollman, A. Physiological variations in the cardiac output of man. IV The effect of breathing carbon dioxide, and of voluntary forced ventilation on the cardiac output of man Am J Physiol 91:287 1930.
2 Prager S. H and Ayman D Hyperventilation in arteriolar hypertension, J Clin. Invest. 12:335 1933
3. Norlin, G Circulation and forced respiration in man, Skandinav Arch. Physiol. 64:239 1932
4 Brown, E. B J Physiological effects of hyperventilation, Physiol. Rev 33:445 1
5 Burnum, J F Hickam, J B and McI

H D The effect of hypocapnia on arterial blood pressure, Circulation 9:89 1954
6. Gleason W L. Berry J N Mauney F M and McIntosh, H. D The hemodynamic effects of hyperventilation (Abstract) Clin. Res. 6:127 1958.
7 Richardson, D W Wasserman, A. J and Patterson, J L. General and regional circulatory responses to change in blood pH and carbon dioxide tension, J Clin. Invest 40:31 1961
8. Berry J N Thompson H K. Miller D E., and McIntosh H. D Changes in cardiac output stroke volume, and central venous pressure induced by atropine in man Am. Heart J 58:204, 1959
9 Hamilton, W F Moore, J W Kinsman, J M. and Spurlin, R. O Studies on the circulation. IV Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions Am J Physiol 99:534 1932
10 Barratt Boyes B G and Wood, E. H Hemodynamic response of healthy subjects to exercise in the supine position while breathing oxygen, J Appl. Physiol 11:129 1957
11 Braunwald, E., and Kelly E. R. The effects of exercise on central blood volume in man J Clin. Invest 39:413 1960
12 Mankin, H T and Swan H J C. Arterial dilution curves of T 1824 during rest and exercise Fed. Proc 12:93 1953
13 Kaufmann, G Über Kreislaufzeiten und Blutverteilung bei Arbeit, Cardiologia (Basel) 30:105 1957
14 Nowy H Kikodse, K., and Zöllner N : Über Bestimmungen des Herzminutenvolumens und zentralen Blutvolumens in Ruhe und bei körperlicher Arbeit mit Hilfe der Farbstoff methode, Ztschr Kreislaufforsch 46:382, 1957
15 Mitchell, J H., Sproule, B J and Chapman, C B The physiological meaning of the maximal oxygen intake test, J Clin. Invest 37:538, 1958
16. Mitchell, J H Sproule, B J., and Chapman C.B : Factors influencing respiration during heavy exercise J Clin Invest. 37:1693, 1958.
17 Roncoroni, A. J Aramendia P Gonzalez R. and Taquini, A C "Central" blood volume in exercise in normal subjects, Acta physiol latinoam 9:55 1959
18 *Marshall, R. J., and Shepherd, J T* Interpretation of changes in "central" blood volume and slope volume during exercise in man, J Clin. Invest. 40:375 1961
19 Gleason, W L Bacos, J M Miller D E., and McIntosh H D A major pitfall in the interpretation of central blood volume (Abstract) Clin Res. :227 1958
20 Gleason, W. L. Personal communication
21 Eckstein J W Hamilton, W K., and McCammond, J M Pressure-volume changes in the forearm veins of man during hyperventilation, J Clin Invest 37:956 1958
22. Eckstein J W., and Hamilton W K. Changes in transmural central venous pressure in man during hyperventilation J Clin. Invest. 37 1537 1958.

Case report

Syndrome of levocardia, multiple cardiac defects, situs inversus, and absent spleen

A case report

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History and physical findings

Y. A., a female infant, was admitted to Children Hospital when she was 7 months old. She had had recurrent attacks of cough, dyspnea, an increase in the force of the heartbeat, and had failed to thrive. History revealed that the heart had been persistently rapid and strong since birth. The child was noticed to be tachypneic, but more so after coughing or crying.

The parents were first cousins. The mother's pregnancy and delivery had been uneventful. The child was breast fed until the age of 5 months, when mixed feeding was begun. She supported the head at 3 months, but was unable to sit down by the age of 7 months. There was no similar condition in other siblings.

Examination revealed a wasted child who weighed 5.0 kilograms. The temperature was 37.2, and the pulse rate was 200. Femoral and dorsalis pedis pulses were felt. The blood pressure was 100/70 mm. Hg. The respiratory rate at rest was 74 per minute.

No cyanosis was evident, but a mild tinge was noticed after severe crying. The eyes were puffy and the extremities showed peripheral edema.

Examination of the heart showed no precordial bulge, the apex was in the fifth left intercostal space at the mid-clavicular line, and was right ventricular in character. A systolic thrill and a harsh pansystolic murmur were audible over the lower precordial region, maximal at the fourth left parasternal space. The second pulmonary sound was weak and single.

The liver was felt on the left side, two finger breadths below the costal margin. The spleen could not be felt.

Investigations

ROENTGENOGRAPHIC FINDINGS. A plain x-ray film of the heart in the posteroanterior view (Fig. 1) showed a gross enlargement, with a cardiothoracic ratio of 0.8. The base was narrow. Vascularity of the lungs was markedly diminished. In the left anterior oblique view the right ventricle was much enlarged. The left border was superimposed over the spine. Whether the left ventricle was enlarged or was pushed by an enlarged right ventricle was difficult to assess. The right anterior oblique view showed no enlargement of the left atrium.

ANGIOCARDIOGRAPHY. The film taken immediately after the injection showed simultaneous opacification of right ventricle, aorta, and pulmonary vessels.

X-RAY FILM AFTER A BARIUM MEAL. This film showed a right-sided stomach with a hiatus hernia. The liver was situated on the left side.



Fig. 1. Huge cardiac enlargement with narrow vascular pedicle. Note the marked pulmonary ischemia.

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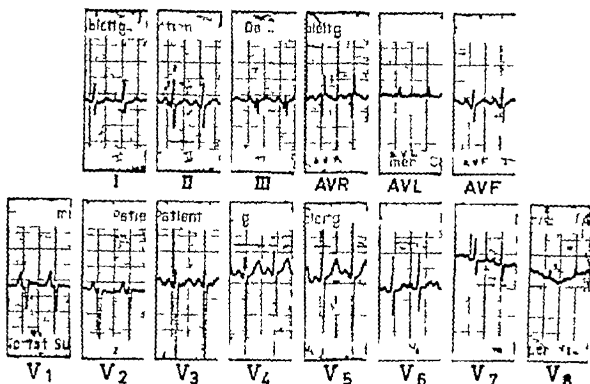


Fig. 2. The electrocardiogram.

ELECTROCARDIOGRAPHY (Fig. 2). The standard leads showed left axis deviation and upright P waves. Unipolar limb leads showed the heart to be horizontal, with marked clockwise rotation. Precordial Leads $V_{1,2,3}$ showed rS and high peaked P waves. The transitional QRS complex appeared in Leads V_4. No Q waves were evident over the left precordium. Lead V_8 showed a small R.

BLOOD EXAMINATION. The concentration of hemoglobin was 100 per cent (14.5 Gm.). The red blood cell count was 4,450,000; reticulocytes, 7 per cent. The mean corpuscular volume was 105 cubic microns; mean corpuscular hemoglobin, 32.5 micromicrograms; mean corpuscular hemoglobin concentration, 30 Gm. per cent. The leukocyte count was 23,000 per cubic millimeter; granulocytes, 30 per cent; lymphocytes, 64 per cent; monocytes, 4 per cent; eosinophils, 2 per cent. There was one normoblast per 100 leukocytes.

Heinz bodies were numerous and amounted to 16 per cent. Not many Howell-Jolly bodies were noted.

COURSE. The child's course in the hospital was progressively downhill. She developed congestive heart failure and died at the age of 8 months.

NECROPSY FINDINGS. Autopsy revealed a generalized anasarca, symmetrical trilobed lungs, complete situs inversus of the abdominal viscera, absence of spleen, and a hiatus hernia.

The heart was left-sided, with the apex at *the left* anterior axillary line. It weighed 72 grams. There was only one atrium and one ventricle, and these communicated through a common atrioventricular canal. *The atrium was greatly distended and hyper*trophied, and the septum was represented by a cord like band (Fig. 3). Superior and inferior vaxue cavae entered the right side in the normal fashion. There were only two pulmonary veins which entered the atrium anteriorly. The single ventricle was hypertrophied (1 cm. in thickness). From its apical part a *thick papillary muscle (proved histologically) arose* and simulated a septum. To the left of this there was a vertical *narrow space* which gave a false impression of atrophic left ventricle. The aorta was dextroposed and lay anterior to the pulmonary artery. The aortic cusps were normal, whereas the pulmonary ones showed a severe stenosis (Fig. 4). *The atrioventricular* valve was separated into three cusps which were rudimentary and contracted.

Discussion

The triad of agenesis of the spleen, defects of the heart and large vessels, and situs inversus is a rare condition. It appears to represent about 1 per cent (21 in 2,224 cases in the combined series of Campbell and Forgacs[1] and Donzelot and D'Allaines[2]) of the cases of congenital heart disease.

Recently, the clinical diagnosis of absence of the spleen could be arrived at on the basis of the spontaneous and continuous formation of Heinz bodies in the



Fig. 3. Interventricular septum is represented by a cord-like band (arrow). The ventricle in the upper right half of the photograph is the back view of the anterior portion.



Fig. 4. *A*, Aorta, dextroposed and showing normal cusps of its valve. *B*, Rod inserted into the stenosed pulmonary trunk. Note the hypertrophy of the myocardium of the single ventricle.

erythrocytes.[3-6] In the present case there was a heavy formation of Heinz bodies (16 per cent) and autopsy confirmed the absence of the spleen.

Trilobed lungs, hiatus hernia, and the cardiac defects which were found in the present case are in accord with the findings in most reported cases. The cardiac malformations in the syndrome were nearly always identical: severe defects of the septa which are either entirely absent or rudimentary. The atrioventricular valve leaflets are absent or rudimentary. Functionally, a bilocular heart is observed in most instances. The origin of the large arteries is always modified; rotation anomalies of the heart and large vessels and anomalies of the large veins are common.[7]

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REFERENCES

1. Campbell, M., and Forgacs, P.: Levocardia with transposition of the abdominal viscera, Brit. Heart J. 15:401, 1953.

2. Donzelot, E., and D'Allaines, F. Traité des cardiopathies congénitales, Paris, 1954, Masson et Cie.
3. Gasser, C., and Willi, H. Spontane Innenkörperbildung bei Milzagenesie, Helvet. paediat. acta 7:369, 1952.
4. Willi, H., and Gasser, C. The clinical diagnosis of the triad spleen agenesis, defects of the heart and vessels, and situs inversus, Neonatal Studies 4:25, 1955.
5. Bush, J. A., and Ainger, L. E. Congenital absence of spleen with congenital heart disease, Pediatrics 15:93, 1955.
6. Polhemus, D. W., and Schafer, W. B.: Absent spleen syndrome. Hematologic findings as an aid to diagnosis, Pediatrics 24:254, 1959.
7. Gasser, C. Heinz body anemia and related phenomena, J. Pediat. 54:688, 1959.

Review

Circulatory effects of sympathomimetic amines

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Sympathomimetic amines have been used more or less empirically in the treatment of hypotension The need for such empiricism is disappearing because of new understanding of circulatory physiology and pharmacology and the elucidation of the pathophysiologic mechanisms which cause blood pressure to fall. The subject remains complex however because of the large number of synthetic agents which have different actions and circulatory effects. The situation is becoming even more complicated because of the introduction into clinical practice of such drugs as the ganglionic blockers, reserpine, guanethidine, bretylium, thiazide diuretics, anticholinergic agents and others which have important interactions with the pressor amines.

We shall discuss these matters briefly and review some of the conditions under which the responses to the pressor amines are enhanced or diminished. We hope to provide an integrated and rational background for the use of these agents in the treatment of hypotension.

Pharmacologic considerations

The responses to the administration of pressor amines resemble the responses to the stimulation of adrenergic nerves. Postganglionic adrenergic sympathetic fibers supply the heart and blood vessels, including both arteries and veins.[1] The work of Euler[1-4] Schmiterlow[5] and Burn[6,7] and their co-workers indicates that impulses mediated by these nerves release the neurotransmitter norepinephrine from tissue stores located at or near the nerve endings. Norepinephrine appears to act upon the myocardium and vascular smooth muscle through cellular receptor mechanisms.[8] It increases the tone of arteries and veins[9] and produces positive inotropic and chronotropic effects on the heart.[10]

Many pressor amines have been synthesized Their chemical structure is similar to that of the naturally occurring catecholamines epinephrine and norepinephrine.[11] The basic compound consists of an aromatic group (benzene ring) and an aliphatic side chain with an amino group (ethylamine) The introduction of methyl hydroxyl or methoxy groups on the aromatic ring or on the side chain produces the various pressor amines. The mode of action and the duration and the intensity of the effects of each amine depend on the type and position of the substitutions.[12,13] According to current theories based on animal experiments the pressor amines fall into two general categories The first

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includes those which act indirectly on the effector organs by liberating norepinephrine from tissue stores. Ephedrine[22,24,25] tyramine[22,24] methamphetamine,[22-25] and mephentermine[22,25] appear to act in this fashion. Their effects should resemble those of norepinephrine. They may be ineffective in the absence of tissue norepinephrine. This has been demonstrated after prolonged treatment of animals with reserpine.[22,17] Drugs in this category are stable. Some of them may be given orally. Although their pressor effect is less than that of amines in the second category their action usually lasts longer. Some of them are potent stimulators of the central nervous system.[11] The second category includes the naturally occurring catecholamines epinephrine,[22,14,23] norepinephrine[22,24,23] and dopamine[23] and the synthetic pressor amines phenylephrine[22,24,23] and methoxamine.[22,23] They act directly on receptors in the myocardium or vascular smooth muscle. The lack of tissue norepinephrine does not reduce their effectiveness; it may enhance it.[6,7,22,14] Other pressor amines like metaraminol[22] Propadrine,[22,24] and possibly methoxamine[23] appear to act directly on receptors besides releasing norepinephrine. Recent reports indicate that ephedrine may have a direct effect in addition to its indirect action.[24,22,23]

Metabolism of epinephrine and norepinephrine. Nearly all circulating norepinephrine comes from tissues supplied by postganglionic adrenergic nerves whereas epinephrine comes from the adrenal medulla. Small amounts of these catecholamines are excreted by the kidneys.[25] Most of them are inactivated enzymatically by the liver.[25] The principal metabolic end product is 3-methoxy-4-hydroxy mandelic acid.[25,26] Two enzyme systems are involved in their metabolism. The catechol-o-methyl-transferase system appears to be the principal one; the monoamine-oxidase system is of less importance.[25-27] Many types of drugs alter the rate of metabolism of these hormones.[27] The psychotropic drugs reserpine, chlorpromazine and imipramine speed the metabolism of epinephrine and norepinephrine whereas catechol-o-methyl-transferase inhibitors such as pyrogallol block it. Until recently, it was believed that the synthetic amines acted by inhibiting monoamine oxidase. Monoamine-oxidase inhibition with iproniazid, however, does not affect the rate of disappearance of epinephrine and norepinephrine. Axelrod and Tomchick[27] showed that the synthetic amines actually increase the rate of metabolism of the catecholamines. This effect is not caused by enhancing catechol-o-methyl-transferase activity. Presumably, the synthetic amines act by preventing the protective binding of catecholamines in the body, thus exposing them to enzymatic attack and rapid destruction.[27] Such a mechanism could explain their ineffectiveness after depletion of endogenous catecholamines. It supports the hypothesis of Burn and Rand[7,22] that many of the synthetic amines act by liberating the natural hormone from its storage sites.

After the administration of monoamine-oxidase inhibitors to man the pressor effects of methoxamine, norepinephrine and its biologic precursor dopamine were augmented.[28] The potentiation of dopamine alone was directly related to enzyme inhibition. Inhibition of catechol-o-methyl-transferase has been shown to potentiate the effects of epinephrine and norepinephrine in animals.[29] It is apparent that the metabolism of endogenous norepinephrine is related intimately to the action of synthetic pressor amines. This has important implications because of the increasing use of psychotropic, antihypertensive, and other drugs which affect the metabolism of endogenous catecholamines.

Depletion of tissue catecholamines and supersensitivity. Prolonged administration of reserpine enhances the effect of exogenous norepinephrine.[22,3,29] This phenomenon is associated with depletion of tissue stores of endogenous *norepinephrine by* reserpine.[7,22] Increased responsiveness to norepinephrine is seen also after postganglionic denervation[22] and the administration of the new antihypertensive compound guanethidine.[30,34] Both denervation[11,22] and the administration of guanethidine[34] deplete the tissues of catecholamines. In contrast to the increased response to norepinephrine the pressor responses to tyramine,[22,24,22] ephedrine[22,3,22,22] methamphetamine[22-22,22] and mephentermine[22,3] are suppressed after depletion. Such amines

might not be effective in patients who are receiving reserpine or guanethidine

Increased sensitivity to norepinephrine which is not related to depletion of tissue stores has been observed during ganglionic blockade,[37] immediately after intravenous injections of guanethidine[33] and after administration of bretylium[33] Bretylium is a new antihypertensive compound which inhibits postganglionic sympathetic transmission.[39-41] It may act by blocking the action of acetylcholine which is released at sympathetic nerve terminals.[42] A new concept that adrenergic sympathetic fibers may first release acetylcholine which in turn liberates norepinephrine from tissue stores is suggested by the experimental work of Burn.[42,43] Guanethidine like bretylium blocks postganglionic sympathetic transmission long before its catecholamine-depleting effect is seen [43,44] Whether the increased sensitivity to norepinephrine results from inhibition of normally operating compensatory reflexes is uncertain [37,44,45]

Receptor theory and reversal of epinephrine effect Sympathetic-nerve stimulation and the sympathomimetic amines produce both excitatory and inhibitory responses. Ahlquist[8] suggested that there may be two types of adrenotropic receptors (1) the alpha receptors which subserve excitatory responses as vasoconstriction and (2) beta receptors which are involved in vasodilatation cardiac acceleration and augmentation of cardiac contractility Epinephrine stimulates both alpha and beta receptors but appears to have a greater affinity for beta receptors. After the administration of the adrenergic blocking drugs phentolamine and Dibenamine which block alpha receptors only epinephrine causes vasodilatation instead of vasoconstriction This reversal is probably the result of unmasking the effects of beta receptor stimulation.[47] The myocardial stimulating effect of sympathomimetic amines mediated through beta receptors is not suppressed by adrenergic blocking drugs.[47]

Dichloroisoproterenol blocks the effects attributed to beta-receptor stimulation.[48] It reduces the inotropic and vasodilator effects of epinephrine.[49] These observations support the receptor theory and suggest that beta receptors in the heart are functionally homologous to the inhibitory beta receptors of blood vessels. [49]

Electrolytes and adrenocortical hormones Increased pressor activity of catecholamines has been observed after treatment with adrenocortical hormones.[50] This potentiation appears to be mediated through alterations in transcellular electrolyte gradients.[51] The diminished pressor[52] and vasoconstrictor[53,54] responses to infusions of norepinephrine after the administration of chlorothiazide are thought also to be related to their effects on cellular electrolytes A great deal of experimental evidence establishes the fact that changes in the concentration of various cations affect vascular reactivity to pressor substances.[55,56]

Physiologic considerations

The height of the arterial pressure depends primarily upon the rate of blood flow into the arteries (the cardiac output) and the resistance to flow from them [58] Blood pressure may fall because of reduced cardiac output or reduced peripheral resistance or both In clinical practice it is common to attribute hypotension regardless of the disease process with which it is associated to decreased peripheral resistance and loss of arterial tone Frequently the reduced output is regarded as a contributing but secondary phenomenon caused by reduced coronary perfusion which results from the fall in aortic pressure In many cases the reduced cardiac output may be a primary rather than a secondary event in the development of the hypotension A fall in cardiac output could result from reduced contractility of the myocardium [60-62] It could result also from reduced venous return secondary to loss of venomotor tone [63-65] obstruction to the return of blood to the heart [67,68] or hypovolemia Loss of arteriolar tone may accompany the fall in output [64,69,70]

The syndrome characterized by weakness pallor prostration oliguria confusion and arterial hypotension is called shock.[71] It may be caused by such diverse conditions as myocardial infarction hemorrhage or bacteremia. That reduced cardiac output is common to most pa[illegible] of the synd ome and that irrev[illegible] and death are in tiated at lo[illegible]

by impaired flow of blood to vital organs is generally agreed. Despite this fact, the often expressed goal in the treatment of many hypotensive states is restoration of blood pressure with drugs which cause arteriolar constriction, the rationale being that simply restoring pressure will insure adequate perfusion of the body. Restoration of arterial pressure, however, is not always accompanied by clinical improvement. If hypotension is caused by a primary reduction in cardiac output, clinical improvement would not be expected regardless of the height of the arterial pressure unless output is restored. Perhaps a more desirable therapeutic goal in many cases of hypotension would be restoration of arterial pressure *and* cardiac output.[72] When a pressor amine is selected for use in hypotension, consideration should be given to the pathophysiologic mechanisms which led to the fall in blood pressure in the first place and to the effects of the amine in question on the veins and heart as well as on the peripheral arteries.

Epinephrine (*Adrenalin*). Cardiac output increases with the administration of epinephrine; stroke volume also increases and there is usually an increase in heart rate.[73,74] Systolic pressure increases and diastolic pressure remains unchanged or increases slightly. There is a moderate increase in mean blood pressure but peripheral resistance falls.[73,74] Blood flow through the muscles of the forearm and calf increases,[75] whereas the flow through skin and mucous membranes decreases.[76] Venous construction has been demonstrated in the extremities,[77,78] and there is evidence that such constriction may shift appreciable quantities of blood centrally.[79] Peripheral venous[79] and right atrial[80] pressures increase. Coronary,[81] cerebral,[82,83] and splanchnic[84] blood flow increase, whereas renal blood flow decreases.[86,87]

The increase in heart rate is presumably the result of the direct action of epinephrine on the sinoatrial node. However, the increase in cardiac output is not simply the result of tachycardia. The drug also increases the force of myocardial contraction. This has been observed repeatedly in dogs[19,55] and was confirmed recently in human subjects.[89] The increased pressure in the atria, which must result in part from venous constriction, would tend to increase ventricular filling, which in turn would favor an increase in cardiac output. The available evidence indicates that epinephrine raises blood pressure primarily by increasing output. Its over-all vasoconstrictor effect appears to be less than that of norepinephrine[1] and other pressor amines.[90]

Norepinephrine (*Levophed*). Norepinephrine and epinephrine have similar actions on the heart. Both increase the rate as well as the force of myocardial contraction in dogs[19,88] and man.[89] When given intravenously to normal men, however, norepinephrine causes cardiac slowing and either no change or a slight decrease in cardiac output.[73,74,91,92] Stroke volume, arterial blood pressure, and peripheral resistance increase. The bradycardia is thought to be of reflex origin, mediated over vagal pathways since it is blocked by atropine.[74] The discrepancy between cardiac output responses to epinephrine and those to norepinephrine has caused some confusion since both substances have similar inotropic and chronotropic effects in isolated heart preparations. This confusion has been resolved by recent work which demonstrated that norepinephrine increased cardiac output in human subjects after they had been treated with tetraethylammonium bromide or atropine.[93] In normal subjects the difference between cardiac output responses to epinephrine and those to norepinephrine appears to result from the peripheral vascular effects of these amines. Norepinephrine has a more potent peripheral vasoconstrictor effect, and it causes greater elevation in blood pressure than does epinephrine.[73] The result is that norepinephrine causes more intense reflex bradycardia. Thus, the negative chronotropic effects of the vagal reflexes mask the direct stimulating effects of norepinephrine and cardiac output changes very little. Norepinephrine might be expected to increase cardiac output if hypotension were present initially or if the vagal regulatory reflexes were suppressed.

Infusion of norepinephrine increases pulmonary arterial and capillary[94] pressures.[91,95] These increases were attributed primarily to engorgement of the blood vessels of the lung from systemic venous

constriction rather than from constriction of pulmonary vessels.[illegible] This seems reasonable since norepinephrine increases central blood volume in dogs[illegible] and causes peripheral venous constriction and shifts of blood from the extremities in man.[74] There have been other demonstrations of peripheral venous constriction with norepinephrine in man[illegible] and it is clear from animal experiments that venous constriction redistributes blood centrally.[illegible] Infusion of norepinephrine decreases blood flow in the muscles of the extremities.[illegible] Renal,[illegible] splanchnic,[illegible] and cerebral[illegible] blood flows also decrease, whereas coronary flow[illegible] increases. Cerebral blood flow increases when norepinephrine is given to subjects made hypotensive by ganglionic blocking drugs.[104]

Since norepinephrine has a generalized constrictor action on the veins, and since it increases the force of myocardial contraction it might be used to restore cardiac output and arterial pressure in hypotensive states in which the reduced output is secondary to venous pooling or loss of myocardial contractile force. Because of its arterial constrictor action it might also be used in conditions in which the hypotension is the result of decreased peripheral resistance.

Metaraminol (Aramine). Metaraminol is a potent pressor agent. Its effects in man resemble those of norepinephrine more closely than do those of many of the other pressor amines. It has a positive inotropic effect on the heart.[illegible] When given intravenously to a normal man it causes increases in both systolic and diastolic blood pressures and marked cardiac slowing.[illegible] Cardiac output remains essentially unchanged and peripheral resistance increases. When bradycardia is prevented by atropine metaraminol causes output to increase markedly.[illegible] In this respect it is much like norepinephrine.[illegible]

Metaraminol reduces renal blood flow in normal man but the renal vasoconstriction appears to be much less than that produced by norepinephrine.[illegible] It causes slight reductions in cerebral blood flow in normotensive subjects but its administration is associated with sharp increases in cerebral flow after the subjects are made hypotensive by ganglionic blocking agents.

Metaraminol causes contraction of smooth muscle in strips of peripheral veins taken from dogs.[illegible] It appears to have similar actions on the veins in vivo since it diminishes the reductions in intrathoracic blood volume and cardiac output which occur with positive pressure breathing in anesthetized dogs.[67, illegible]

Mephentermine (Wyamine). There has been confusion about the physiologic effects of mephentermine. One of the first reports on its cardiovascular effects in human subjects described increases in systolic and diastolic pressures but essentially no change in cardiac output.[illegible] Similar observations were made in dogs by the same investigators[illegible] and it was concluded that mephentermine increased blood pressure by increasing peripheral resistance. Subsequent investigations have revealed that the drug has distinct inotropic and chronotropic effects on the hearts of dogs,[illegible] with little effect on peripheral resistance.[illegible] Arterial constriction has been observed in the dog foreleg.[illegible] To our knowledge the original observations on cardiac output in man have not been confirmed. Output has been demonstrated to increase regularly in both normotensive and hypotensive dogs under a variety of conditions.[illegible] Coronary blood flow increases in dogs,[illegible] and there is minimal vasoconstriction in the kidney.[illegible]

In man mephentermine increases the force of myocardial contraction[illegible] and increases cerebral blood flow without changing cerebral vascular resistance.[illegible] Blood flow in the forearm decreases initially with moderate doses but returns to control levels within 10 minutes after intravenous injection.[illegible] Blood pressure and peripheral resistance increase.[illegible]

Unchanged or increased resistance in the presence of increased blood pressure means that there must have been increases in vascular tone in the brain and forearm. Observations on the peripheral circulation and on myocardial function in man suggest that mephentermine probably increases arterial pressure by increasing cardiac output and peripheral resistance. It is our impression however that the peripheral constrictor actions of mephentermine are relatively weak.

Ephedrine (Ephedrine). Ephedrine

introduced into clinical practice about 1925 and it has remained as one of the commonly used pressor amines. Its cardiovascular effects are similar to those of epinephrine, but its onset of action is slower and its effects are more prolonged.[99] After intramuscular injection there are increases in cardiac output and systolic blood pressure, without much change in diastolic pressure. Peripheral resistance may increase[99] or decrease.[114] Heart rate changes very little with therapeutic doses, but there may be reflex bradycardia at the peak of the pressor response. Stroke volume usually increases. Venous pressure increases, and the veins of the forearm constrict sufficiently to push blood from the extremities.[114] Ephedrine produces vasoconstriction in the finger[118] and has only a mild or insignificant vasoconstrictor effect on the kidney in therapeutic doses.[99, 117] It increases blood flow in the forearm.[119]

No data are available in regard to the direct effects of ephedrine on heart muscle in man but it increases the force of myocardial contraction in dogs.[10] Vasoconstriction in the splanchnic bed has been observed in animals.[11] Coronary blood flow increases in dogs.[119, 120]

Methamphetamine (*Methedrine*). Chemically methamphetamine is similar to ephedrine. Its cardiovascular effects in man have not been studied extensively. However, it appears to resemble ephedrine in its actions, although it is a somewhat less potent pressor agent.[11] It has potent central nervous-system stimulating properties.[11] The drug is reported to increase cardiac output and total peripheral resistance and to decrease muscle blood flow slightly.[122] It has little effect on heart rate although bradycardia may be seen initially. This bradycardia is prevented by atropine and after atropine methamphetamine causes muscle blood flow to increase.[119] Methamphetamine like ephedrine causes systolic pressure to rise sharply, leaving diastolic pressure relatively unchanged.[111] In anesthetized subjects it increases renal blood flow; under the same conditions, epinephrine and norepinephrine cause renal blood flow to decrease.[123] The drug also increases peripheral venous pressure and causes venous constriction in the forearm.[124]

Phenylephrine (*Neo-Synephrine*). Phenylephrine is a potent vasoconstrictor. When given to man it increases both systolic and diastolic blood pressures and causes marked bradycardia. Circulation time increases and cardiac output decreases slightly; peripheral resistance increases.[125, 126] In the atropinized subject there is some increase in heart rate and the pressor effect is augmented.[126] This suggests that the drug may also have a positive inotropic effect. There are no direct measurements of the inotropic effects of phenylephrine on the human heart. Its effect on the contractile force of the dog heart is minimal.[10] Other studies show that its direct cardioaccelerator action is minimal also.[127] The bradycardia in man is mainly the result of reflex depression of the sinoatrial node.[128] Phenylephrine causes a moderate fall in renal blood flow in man.[129] It also causes vasoconstriction in the finger.[118]

Methoxamine (*Vasoxyl*). The pressor effect of methoxamine appears to be due principally to vasoconstriction.[99] The drug has no significant inotropic effect on the human[97] or dog[10] heart. In man it increases both systolic and diastolic blood pressures and causes more renal vasoconstriction for a given increase in blood pressure than does either norepinephrine or metaraminol.[130] Peripheral venous pressure increases after parenteral administration, but there is little effect on venous tone in the forearm.[124] Methoxamine does not increase ventricular rate in patients with heart block nor does it prevent the cardiac standstill induced by stimulation of the carotid sinus.[131] In animals the bradycardia which follows its administration appears to be caused primarily by reflexes activated by the increase in blood pressure.[132]

In dogs methoxamine given intravenously causes a fall in cardiac output even as arterial pressure is rising.[10, 31] These changes are associated with increases in left and right atrial and pulmonary arterial pressures. As the infusions of methoxamine are continued, arterial pressure begins to fall below the peak values previously reached. This fall in pressure appears to be the result of ventricular failure rather than tachyphylaxis to the vasoconstrictor effect of the methoxamine.[133] Methoxamine has

a depressing action on the myocardium of dogs after being injected into the coronary artery[136] and it prolongs the action potential as well as the refractory period and slows atrioventricular conduction[136]

Clinical considerations

In this section we shall consider briefly the pathophysiology of several hypotensive states in an attempt to provide a rational background for the use of various pressor amines. We shall discuss also some of the factors which affect the responses to these drugs.

Hypotension associated with ganglionic blockade Initial studies on the hemodynamic effects of ganglionic blocking drugs in man demonstrated that the hypotension was caused primarily by a fall in cardiac output[87,140] This fall in output could be attributed in part to pooling of blood in peripheral veins because of reduced venous tone.[illegible] Subsequent investigations showed that reduction in myocardial function[illegible] and loss of arterial tone[illegible] contribute also to the fall in blood pressure In hypotension associated with ganglionic blockade it would be reasonable to employ a vasopressor which causes both venous and arteriolar constriction and exerts a positive inotropic effect on the heart. Norepinephrine has all these properties If the situation does not require norepinephrine then metaraminol ephedrine methamphetamine and mephentermine would be appropriate. These substances may be given subcutaneously They have longer action than does norepinephrine.

Spinal shock The hypotension which accompanies high spinal anesthesia is associated with reduced peripheral arterial tone and a fall in cardiac output[illegible] The fall in output is attributed to the result of anesthetic blockade of cardiac sympathetic fibers.[illegible] This would explain the bradycardia which is often observed There is evidence that some cardiac sympathetic fibers arise from levels below that of the fourth thoracic segment[illegible] a level which is frequently reached in spinal anesthesia. It has been suggested that the reduced output may be caused in part by venous pooling and reduced venous return[illegible] since a fall in venous pressure accompanies the hypotension[144] A pressor amine which constricts veins and arteries and which has a positive inotropic effect on the heart would be appropriate for spinal shock Methoxamine and phenylephrine might not be effective because they cause arterial constriction without increasing cardiac output.

Cardiogenic shock The pressor amines are very useful in the treatment of cardiogenic shock[illegible] but there has been controversy about the type of drug which should be employed[illegible] Some have advocated the use of the pure vasoconstrictor amines such as phenylephrine and methoxamine whereas others favor the use of norepinephrine metaraminol and mephentermine, which have inotropic effects on the heart in addition to their vasoconstrictor properties.[illegible]

It has been proposed that the hypotension which accompanies acute myocardial infarction should be treated with vasopressor drugs to elevate aortic pressure and improve coronary perfusion[illegible] It is true that reduced coronary perfusion contributes to the very serious effects of prolonged hypotension. The induction of vasoconstriction might be appropriate treatment if the hypotension were caused only by loss of arterial tone However there is evidence which indicates that the low blood pressure results largely from the reduced cardiac output[illegible] which is caused by impaired myocardial contractility[illegible] Experimental studies indicate that myocardial contractility may be increased by metaraminol even in the presence of reduced coronary flow[illegible] Clinical observations suggest that norepinephrine may be more beneficial than phenylephrine in cardiogenic shock.[illegible] For these reasons we subscribe to the opinion that an amine which increases the force of myocardial contraction should be used in cardiogenic shock rather than one which exerts its effects only by arterial constriction[illegible] Better perfusion of vital organs would be expected from an increase in both perfusion pressure *and* total blood flow rather than from an increase in perfusion pressure alone

Frequently patients with cardiogenic shock after myocardial infarction improve temporarily when norepinephrine is administered and then go into congestive heart failure. It appears that the da

recently that saturation of vascular stores with norepinephrine may reduce the availability of receptors for circulating catecholamines so that vascular tone is decreased.[19] The administration of a pressor agent such as methamphetamine which releases norepinephrine from storage sites, has been recommended as appropriate treatment for such secondary hypertension.[19,154] Obviously the precise cause of the postinfusion hypotension is not clear. Regardless of the cause, however, treatment with a vasopressor agent other than epinephrine or norepinephrine deserves trial.

Hypoxia and acidosis. Animal experiments and observations on patients have demonstrated that the effects of pressor amines on the heart and blood vessels are reduced during hypoxia and acidosis.[187,188] This is of considerable clinical importance. Many patients in shock are weak and dehydrated, their lungs are hypoventilated, and their arterial blood oxygen saturation is reduced. Often there is azotemia and poor perfusion of the tissues with oxygenated blood. Reflex compensatory and homeostatic mechanisms are absent or impaired. Acidosis is often present in such circumstances and responses to pressor amines are reduced. Restoration of normal blood pH by intravenous infusions of sodium lactate may be accompanied by renewed responsiveness to the pressor agents.[7,72]

Complications of therapy with pressor amines. Hepatic necrosis,[42] renal necrosis,[19] gangrene of the extremities,[188] focal myocarditis, subpericardial hemorrhages, and necrotizing arteritis of the gastrointestinal tract[58] have been reported to follow infusions of pressor amines. The pathogenesis of these lesions is not clear. It must be remembered, however, that the state of shock itself may cause necrosis of various tissues.[79] These complications *should not prevent the use of pressor amines* in situations in which they are truly indicated. The complications are not common, and it has not been established that their occurrence in patients is related primarily to the use of the pressor drugs. The lesions in patients are usually seen at postmortem examination. In our experience they have been seen most frequently in patients who were very ill with profound alterations in blood volume and body fluids and electrolytes at the time treatment with pressor amines was instituted.

Ischemic necrosis with local sloughing of tissues sometimes follows accidental extravasation of norepinephrine. This has been prevented by local injection of phentolamine at the site of extravasation.[197] Recently the addition of phentolamine to the infusion has been recommended as a prophylactic measure. This has been reported to prevent ischemic necrosis without altering the pressor response.[193] It is a good practice to infuse through a polyethylene tube inserted well into the vein through a large-bore needle. A change of infusion sites is important if prolonged treatment is necessary. The danger of thrombosis and necrosis is reduced if veins in the arm rather than in the leg are used. The addition of heparin to the infusion solution lowers the incidence of local venous thrombosis.[[illegible]]

Adrenal steroids. Experimental evidence suggests that in normotensive and hypertensive animals and in normotensive man adrenocortical steroids potentiate the pressor effects of catecholamines.[4] When steroids were given for treatment of hemorrhagic or traumatic shock, however, they failed to produce the expected salutary results on blood pressure.[[illegible]] Lansing[[illegible]] observed that the addition of hydrocortisone to norepinephrine for the treatment of hemorrhagic shock in the rat had no beneficial effects beyond those of norepinephrine alone. From presently available information it seems to us that the routine use of adrenal steroids in conjunction with pressor amines for the treatment of shock in general is not warranted. However, it must be mentioned that their use should be considered seriously in bacteremic shock. Spink and Vick[197] demonstrated that the combination of metaraminol and hydrocortisone was more effective in restoring the blood pressure in endotoxin shock in dogs than was either of these agents when used alone. Spink[[illegible]] recommends the use of hydrocortisone in bacteremic shock in human beings.

CONCLUDING COMMENTS. When one considers the physiopathology of the various

conditions in which a vasopressor drug might be used. It becomes difficult to find indications for employment of an agent which increases arterial pressure solely by its arterial constrictor effects. In the majority of cases norepinephrine, the same substance which occurs naturally in the body, has properties which are indicated most specifically. Under normal conditions the body responds readily to norepinephrine as well as to a variety of agents which release endogenous norepinephrine from tissue storage sites. In conditions in which the body is depleted of norepinephrine, as may be the case in patients treated with guanethidine or reserpine, the indirect-acting drugs may be expected to have little effect since there is no norepinephrine to release. In cases of depletion, however, the vascular and cardiac receptors are responsive to exogenous norepinephrine. It may be regarded as the most potent of the pressor amines and its rapid onset of action is important in many emergency situations. Under adverse conditions it is the drug most likely to produce a therapeutic response. We believe that norepinephrine should be considered first in most situations in which a pressor amine is to be used. A possible exception is the hypotension which occurs after long infusions of norepinephrine, in which case as Burn[13] and Bromage[14] suggest, a releasing drug may be indicated.

Although we believe it to be good practice to think of norepinephrine first, we do not mean to imply that it is always the drug of choice. In many situations in which the potency of norepinephrine is not required and the intravenous infusion is a disadvantage, metaraminol, ephedrine, mephentermine, or methamphetamine will serve quite satisfactorily. Metaraminol appears to have some advantages, in that it is quite potent and less prone to exhibit tachyphylaxis than are some of the other amines. The central nervous-system stimulating properties of ephedrine and methamphetamine may be desirable in some cases.

It has been our observation that disappointment in the use of pressor amines often results from two things: (1) the idea that the restoration of arterial pressure is the primary goal in the treatment of hypotension and (2) the excessive reliance on the vasopressor drugs even to the exclusion of other forms of treatment. We wish to re-emphasize the fact that the goal in the treatment of most forms of hypotension is the maintenance of total blood flow and perfusion pressure, not restoration of arterial pressure alone. We wish to emphasize also that the vasopressor drugs will be more effective if special attention is given to general measures indicated in the care of ill patients. These include proper diagnosis, the maintenance of an adequate airway and adequate ventilation of the lungs, the use of oxygen, transfusions, treatment of infection, relief from pain, attention to nutrition, and appropriate treatment of fluid and electrolyte problems.

A very important requirement for the future use of pressor amines will be an understanding of their interactions with the wide variety of drugs which have profound effects on autonomic function, for they are being introduced into medical practice to treat many chronic diseases.

REFERENCES

1. Euler, U. S. von: Epinephrine and norepinephrine actions and use in man, Clin. Pharmacol. & Therap. 1:65, 1960.
2. Euler, U. S. von: The presence of a substance with sympathin E properties in spleen extracts, Acta physiol. scandinav. 11:168, 1946.
3. Euler, U. S. von: A specific sympathomimetic ergone in adrenergic nerve fibers (sympathin) and its relations to adrenaline and nor-adrenaline, Acta physiol. scandinav. 12:73, 1946.
4. Euler, U. S. von, and Purkhold, A.: Histamine in organs and its relation to the sympathetic nerve supply, Acta physiol. scandinav. 24:218, 1951.
5. Schmiterlöw, C. G.: Depressor and pressor activity of extracts from the aortic wall of cattle, Acta physiol. scandinav. 15:47, 1948.
6. Burn, J. H., and Rand, M. J.: Action of nicotine on the heart, Brit. M. J. 1:137, 1958.
7. Burn, J. H., and Rand, M. J.: Noradrenaline in artery walls and its dispersal by reserpine, Brit. M. J. 1:903, 1958.
8. Ahlquist, R. P.: A study of adrenotropic receptors, Am. J. Physiol. 153:586, 1948.
9. Haddy, F. J., Fleishman, M., and Emanuel, D. A.: Effect of epinephrine, norepinephrine and serotonin upon systemic small and large vessel resistance, Circulation Res. 5:247, 1957.
10. Goldberg, L. I., Cotten, M. DeV., Darby, T. D., and Howell, E. V.: Comparative heart contractile force effects of equipressor doses of several sympathomimetic amines, J. Pharmacol. & Exper. Therap. 108:177, 1953.

11. Goodman, L. S., and Gilman, A.: The pharmacological basis of therapeutics, ed. 2, New York, 1956, The Macmillan Company.
12. Burn, J. H., and Rand, M. J.: The action of sympathomimetic amines in animals treated with reserpine, J. Physiol. 144:314, 1958.
13. Burn, J. H., and Rand, M. J.: Fall of blood pressure after a noradrenaline infusion and its treatment by pressor agents, Brit. M. J. 1:394, 1959.
14. Maxwell, R. A., Povalski, H., and Plummer, A. J.: A differential effect of reserpine on pressor amine activity and its relationship to other agents producing this effect, J. Pharmacol. & Exper. Therap. 125:178, 1959.
15. Eger, E. I. II, and Hamilton, W. K.: The effect of reserpine on the action of various vasopressors, Anesthesiology 20:641, 1959.
16. Swaine, C. R., Perlmutter, J., and Ellis, S.: Mechanism of action of mephentermine, Fed. Proc. 19:122, 1960.
17. Burn, J. H.: Reserpine and noradrenaline in artery walls, Lancet 2:1097, 1957.
18. Moore, J. I., and Moran, N. C.: The effect of ephedrine on myocardial contractility in dogs pretreated with reserpine, Fed. Proc. 19:111, 1960.
19. Trendelenburg, U., and Fleming, W. W.: Subsensitivity to certain sympathomimetics after pretreatment with reserpine, Fed. Proc. 19:284, 1960.
20. Vendsalu, A.: Studies on adrenaline and noradrenaline in human plasma, Acta physiol. scandinav. 49(Suppl. 173), 1960.
21. Armstrong, M. D., McMillan, A., and Shaw, K. N. F.: 3-Methoxy-4-hydroxy D-mandelic acid, a urinary metabolite of norepinephrine, Biochim. et biophys. acta 25:422, 1957.
22. Sjoerdsma, A., Leeper, L. C., Terry, L. L., and Udenfriend, S.: Studies on the biogenesis and metabolism of norepinephrine in patients with pheochromocytoma, J. Clin. Invest. 38:31, 1959.
23. Axelrod, J.: O-methylation of epinephrine and other catechols in vitro and in vivo, Science 126:400, 1957.
24. La Brosse, E. H., Axelrod, J., and Kety, S. S.: O-methylation, the principal route of metabolism of epinephrine in man, Science 128:593, 1958.
25. Axelrod, J., and Tomchick, R.: Enzymatic o-methylation of epinephrine and other catechols, J. Biol. Chem. 233:702, 1958.
26. Axelrod, J., and Laroche, M. J.: Inhibitor of o-methylation of epinephrine and norepinephrine in vitro and in vivo, Science 130:800, 1959.
27. Axelrod, J., and Tomchick, R.: Increased rate of metabolism of epinephrine and norepinephrine by sympathomimetic amines, J. Pharmacol. & Exper. Therap. 130:367, 1960.
28. Horwitz, D., Goldberg, L. I., and Sjoerdsma, A.: Increased blood pressure responses to dopamine and norepinephrine produced by monoamine oxidase inhibitors in man, J. Lab. & Clin. Med. 56:747, 1960.
29. Wylie, D. W., Archer, S., and Arnold, A.: Augmentation of pharmacological properties of catecholamines by o-methyl transferase inhibitors, J. Pharmacol. & Exper. Therap. 130:239, 1960.
30. Bein, H. J., Gross, F., Tripod, J., and Meier, R.: Experimentelle Untersuchungen über "Serpasil" (Reserpin) ein neues, sehr wirksames Rauwolfia alkaloid mit neuartiger zentraler Wirkung, Schweiz. med. Wchnschr. 83:1007, 1953.
31. Burn, J. H., and Rand, M. J.: The cause of the supersensitivity of smooth muscle to noradrenaline after sympathetic degeneration, J. Physiol. 147:135, 1959.
32. Maxwell, R. A., Plummer, A. J., Povalski, H., and Schneider, F.: Concerning a possible action of guanethidine (SU 5864) in smooth muscle, J. Pharmacol. & Exper. Therap. 129:24, 1960.
33. Abboud, F. M., and Eckstein, J. W.: Effect of guanethidine on forearm vascular responses to graded doses of norepinephrine, J. Lab. & Clin. Med. 56:786, 1960.
34. Kirkendall, W. M., Fitz, A. M., Van Hecke, D. C., Wilson, W. R., and Armstrong, M. L.: Hemodynamic and clinical effects of guanethidine, J. Iowa Med. Soc. 51:69, 1961.
35. Euler, U. S. von, and Purkhold, A.: Effect of sympathetic denervation on the noradrenaline and adrenaline content of the spleen, kidney and salivary glands in the sheep, Acta physiol. scandinav. 24:212, 1951.
36. Cass, R., Kuntzman, R., and Brodie, B. B.: Norepinephrine depletion as a possible mechanism of action of guanethidine (SU 5864), a new hypotensive agent, Proc. Soc. Exper. Biol. & Med. 103:871, 1960.
37. Hass, E., and Goldblatt, H.: Effects of various ganglionic blocking agents on blood pressure and on activity of pressor agents, Am. J. Physiol. 198:1023, 1960.
38. Abboud, F. M., Eckstein, J. W., and Pereda, S. A.: Early potentiation of vascular responses to norepinephrine by intravenous guanethidine, Fed. Proc. 20:517, 1961.
39. Boura, A. L. A., Green, A. F., McCoubrey, A., Laurence, D. R., Moulton, R., and Rosenheim, M. L.: Darenthin: hypotensive agent of new type, Lancet 2:17, 1959.
40. Boura, A. L. A., Copp, F. C., Duncombe, W. G., Green, A. F., and McCoubrey, A.: The selective accumulation of bretylium in sympathetic ganglia and their postganglionic nerves, Brit. J. Pharmacol. 15:265, 1960.
41. Hukovic, S.: The action of sympathetic blocking agents on isolated and innervated atria and vessels, Brit. J. Pharmacol. 15:117, 1960.
42. Burn, J. H.: A new view of adrenergic fibers, explaining the action of reserpine, bretylium and guanethidine, Brit. M. J. 1:1623, 1961.
43. Burn, J. H., and Rand, M. J.: Sympathetic postganglionic cholinergic fibers, Brit. J. Pharmacol. 15:56, 1960.
44. McCubbin, J. W., Kaneko, Y., and Page, I. H.: The peripheral cardiovascular actions of guanethidine in dogs, J. Pharmacol. & Exper. Therap. 131:346, 1961.
45. Page, I. H., and Taylor, R. D.: Augmentation of vasoactive substances by tetraethylam-

monium chloride, Circulation 1 1233 1950.
46 Haas, E., and Goldblatt, H Effects of an antihypertensive drug pentolinium Am. J Physiol. 196 763 1959
47 Nickerson, M., and Gump, W. S. The chemical basis for adrenergic blocking activity in compounds related to Dibenamine J Pharmacol. & Exper Therap. 97:25 1949
48. Powell, C. E., and Slater I. H Blocking of inhibitory adrenergic receptors by a dichloro analogue of isoproterenol, J Pharmacol. & Exper Therap. 122:480, 1958.
49 Moran, N. C., and Perkins M E. Adrenergic blockade of the mammalian heart by a dichloro analogue of isoproterenol, J Pharmacol. & Exper Therap. 124:223 1958
50. Raab W., Humphreys, R. J and Lepeschkin, E. Potentiation of pressor effects of norepinephrine and epinephrine in man by desoxycorticosterone acetate, J Clin. Invest. 29:1397 1950.
51 Raab W Transmembrane cationic gradient and blood pressure regulation Interaction of corticoids, catecholamines and electrolytes on vascular cells, Am. J Cardiol. 4 752, 1959
52. Prerlod, P Bianchi, A Loscalzo, B and Schaepdryver A. F de On the pharmacology of chlorothiazide, with special regard to its diuretic and antihypertensive effects, Arch. internat. pharmacodyn. 118:467 1959
53 Feisal, K. A., Eckstein, J W Horsley A W and Kessling H. H Effects of chlorothiazide on forearm vascular responses to norepinephrine J Appl. Physiol 16:549 1961
54. Eckstein, J W., Pereda, S. A., Abboud, F M and Wendling M The effect of chlorothiazide on cardiac output responses to norepinephrine, Circulation 24:923 1961
55 Friedman S. M Friedman, C. L., and Nakashima, M. Cationic shifts and blood pressure regulation, Circulation Res 5:261 1957
56. Friedman, S., Jamieson, J D and Friedman, C. L. Sodium gradient, smooth muscle tone and blood pressure regulation, Circulation Res. 7:44, 1959
57 Bohr D F Brodie D C and Chew D H Effect of electrolytes on arterial muscle contraction, Circulation 17 746 1958
58. Haddy F J Local effects of sodium calcium and magnesium upon small and large blood vessels of the dog forelimb, Circulation Res. 8:57 1960.
59 Ruch, T C and Fulton, J F Medical physiology and biophysics, ed. 18, Philadelphia, 1960 W B Saunders Company
60. Gorlin, R., and Robin, E. D Cardiac glycosides in the treatment of cardiogenic shock Brit. M. J 1:937 1955
61 Zimmerman, B G Brody M J and Beck, L. Mechanism of the cardiac output reduction by hexamethonium Am J Physiol. 199:319 1960.
62. Eckstein, J W and Horsley A. W The effects of reduced cardiac sympathetic tone on myocardial function, J Clin. Invest. 40:555 1961
63 Alexander R. S: Venomotor tone in hemorrhage and shock, Circulation Res. 3:181 1955.
64. Smith, J R., and Hoobler S. W Acute and chronic cardiovascular effects of pentolinium in hypertensive patients, Circulation 14 1061 1956.
65 Freis, E. D and Rose, J C. The sympathetic nervous system, the vascular volume and the venous return in relation to cardiovascular integration, Am. J Med. 22 175 1957
66. Combes, B Preedy J R. K., Wheeler H O., Hays, R. M and Bradley S E The hemodynamic effects of hexamethonium bromide in the dog with special reference to "splanchnic pooling" J Clin Invest. 36:860, 1957
67 Braunwald, E., Binion J T Morgan, W L., J and Sarnoff S J Alterations in central blood volume and cardiac output induced by positive pressure breathing and counteracted by metaraminol (Aramine) Circulation Res 5:670 1957
68 Morgan W L., Jr., Binion, J T., and Sarnoff S. J Circulatory depression induced by high levels of positive pressure breathing counteracted by metaraminol (Aramine) J Appl. Physiol. 10:26, 1957
69 Trapold J H Role of venous return in the cardiovascular response following injection of ganglion-blocking agents, Circulation Res. 5:444 1957
70 Aviado, D M Hemodynamic effects of ganglionic blocking drugs Circulation Res. 8:304, 1960.
71 Weil, M H Current concepts on the management of shock, Circulation 16 1097 1957
72. Sarnoff S J and Berglund, E. Ventricular function I Starling law of the heart studied by means of simultaneous right and left ventricular function curves in the dog, Circulation 9 706 1954
73 Goldenberg, M Pines, K. L Baldwin E. deF Greene, D G and Roh, C. E The hemodynamic response of man to norepinephrine and epinephrine and its relation to the problem of hypertension, Am J Med 5 792 1948.
74 Barcroft, H and Starr I Comparison of the actions of adrenaline and noradrenaline on the cardiac output in man, Clin. Sc. 10:295, 1951
75 Barcroft H and Konzett, H. On the actions of noradrenaline, adrenaline and isopropyl noradrenaline on the arterial blood pressure heart rate and muscle blood flow in man J Physiol. 110 194 1949
76. Barnett, A. J Blacket R. B., Depoorter A. E., Sanderson, P H and Wilson, G. M The action of noradrenaline in man and its relation to pheochromocytoma and hypertension, Clin Sc 9 151 1950
77 Page, E. B Hickam, J B Sieker H O., McIntosh, H D and Pryor W W Reflex venomotor activity in normal persons and in patients with postural hypotension Circulation 11:262, 1955
78. Eckstein, J W and Hamilton, W K. The pressure-volume responses of human forearm veins during epinephrine and norepinephrine Invest. 36 1663, 1957

79 Glover W. E., Greenfield A. D. M., Kidd B. S. L., and Whelan, R. F.: The reactions of the capacity blood vessels of the human hand and forearm to vasoactive substances infused intra-arterially, J. Physiol. 140:113, 1958.
80 Ranges H. A., and Bradley S. E.: Systemic and renal circulatory changes following the administration of adrenin, ephedrine, and paredrinol to normal man, J. Clin. Invest. 22:68, 1943.
81 Corday E., Williams J. H., de Vera L. B., and Gold H.: Effect of systemic blood pressure and vasopressor drugs on coronary blood flow and the electrocardiogram, Am. J. Cardiol. 3:626, 1959.
82 King B. D., Sokoloff L., and Wechsler R. L.: The effect of l-epinephrine and l-norepinephrine upon cerebral circulation and metabolism in man, J. Clin. Invest. 31:273, 1952.
83 Sensenbach W., Madison L., and Ochs L.: A comparison of the effects of l-norepinephrine, synthetic l-epinephrine, and U.S.P. epinephrine upon cerebral blood flow and metabolism in man, J. Clin. Invest. 32:226, 1953.
84 Bearn, A. G., Billing, B., and Sherlock, S.: The effect of adrenaline and noradrenaline on hepatic blood flow and splanchnic carbohydrate metabolism in man, J. Physiol. 115:430, 1951.
Chasis H., Ranges H. A., Goldring W., and Smith H. W.: The control of renal blood flow and glomerular filtration in normal man, J. Clin. Invest. 17:683, 1938.
Barclay J. A., Cooke W. T., and Kenney R. A.: Observations on the effect of adrenaline on renal function and circulation in man, Am. J. Physiol. 151:621, 1947.
Smythe C. McC., Nickel J. F., and Bradley S. E.: The effect of epinephrine (U.S.P.), l-epinephrine, and l-norepinephrine on glomerular filtration rate, renal plasma flow, and the urinary excretion of sodium, potassium, and water in normal man, J. Clin. Invest. 31:499, 1952.
Kushmer R. F., and Watts T. C.: Role of autonomic hormones on left ventricular performance continuously analyzed by electronic computer, Circulation Res. 5:240, 1957.
Goldberg L. I., Bloodwell R. D., Braunwald E., and Morrow A. G.: The direct effects of norepinephrine, epinephrine, and methoxamine on myocardial contractile force in man, Circulation 22:1125, 1960.
90 Vasko D. M. J.: Cardiovascular effect of some commonly used pressor amines, Anesthesiology 20: 3, 1959.
91 Fowler N. O., Westcott R. N., Scott, R. C., and McGuire J.: The effect of norepinephrine upon pulmonary arteriolar resistance in man, J. Clin. Invest. 30:517, 1951.
92 Tuckman J., and Finnerty F. A., Jr.: Cardiac index during intravenous levarterenol infusion in man, Circulation Res. 7:988, 1959.
93 Wilber J. A., and Brust A. A.: The circulatory and metabolic effects in man of histamine, Mecholyl, tetraethylammonium, and atropine in the presence of circulating epinephrine and norepinephrine, J. Clin. Invest. 37:476, 1958.
94 Patel, D. J., Lange, R. L., and Hecht, H. H.: Some evidence for active constriction in the human pulmonary vascular bed, Circulation 18:19, 1958.
95 Shadle O. W., Moore J. C., and Billig D. M.: Effect of l-arterenol infusion on central blood volume in the dog, Circulation Res. 3:385, 1955.
96. Burch G. E., and Murtadha M.: A study of the venomotor tone in a short intact venous segment of the forearm of man, Am. Heart J. 51:807, 1956.
97 Burch G. E.: Rheoplethysmographic studies of digital venous tone and venous activity, J. Lab. & Clin. Med. 55:342, 1960.
98 Burch G. E., and DePasquale N. P.: The effect of norepinephrine on the digital veins, Am. Heart J. 60:915, 1960.
99 Rashkind, W. J., Lewis, D. H., Henderson, J. B., Heiman, D. F., and Dietrick, R. B.: Venous return as affected by cardiac output and total peripheral resistance, Am. J. Physiol. 175:415, 1953.
100 Rowe J. C., and Freis, E. D.: Alterations in systemic vascular volume of the dog in response to hexamethonium and norepinephrine, Am. J. Physiol. 191:283, 1957.
101 Corcoran A. C., Wagner W. E., and Page I. H.: Renal participation in enhanced pressor responses to noradrenaline in patients given hexamethonium, J. Clin. Invest. 35:668, 1956.
102 Feinberg H., and Katz, L. N.: Effect of catecholamines, l-epinephrine and l-norepinephrine on coronary flow and oxygen metabolism of the myocardium, Am. J. Physiol. 193:151, 1958.
103 Li enas W. R., Moyer J. H., and Chapman D. W.: The cardiovascular and renal hemodynamic effect of Aramine, Am. Heart J. 1:745, 1954.
104 Moyer J. H., Morris G., and Snyder H.: A comparison of the cerebral hemodynamic response to Aramine and norepinephrine in the normotensive and hypotensive subject, Circulation 10:265, 1954.
105 Leonard E., and Sarnoff S. J.: Effect of Aramine-induced smooth muscle contraction on length tension diagrams of venous strips, Circulation Res. 5:169, 1957.
106 Brofman B. L., Hellerstein H. K., and Caskey W. H.: Mephentermine—an effective pressor amine. Clinical and laboratory observations, Am. Heart J. 44:396, 1952.
107 Welch G. H., Jr., Braunwald E., Case R. B., and Sarnoff S. J.: The effect of mephentermine sulfate on myocardial oxygen consumption, myocardial efficiency, and peripheral vascular resistance, Am. J. Med. 24:871, 1958.
108 Borden C., and Haddy F. J.: Comparison of peripheral vascular effects of certain sympathomimetic amines, Clin. Res. 7:337, 1959.
109 Harkey A. W., and Eckstein J. W.: Hemodynamic responses to administration of mephentermine in normotensive and hypotensive dogs, Am. Heart J. 61:85, 1961.

110. West, J. W., Guzman, S. V., and Bellet, S.: Comparative cardiac effects of various sympathomimetic amines, Circulation 16:950, 1957.
111. Mills, L. C., and Moyer, J. H.: The effects of various catecholamines on specific vascular hemodynamics in hypotensive and normotensive subjects, Am. J. Cardiol. 5:652, 1960.
112. Richardson, D. W., Ferguson, R. W., and Patterson, J. L., Jr.: Effects of mephentermine on cerebral metabolism and circulation, J. Pharmacol. & Exper. Therap. 119:219, 1957.
113. Horsley, A. W., and Eckstein, J. W.: Effect of mephentermine on venomotor tone, blood flow and arterial pressure in forearm of man, Proc. Soc. Exper. Biol. & Med. 105:569, 1960.
114. Starr, I., Gamble, C. J., Margolies, A., Donal, J. S., Jr., Joseph, N., and Eagle, E.: A clinical study of the action of 10 commonly used drugs on cardiac output, work and size on respiration, on metabolic rate and on the electrocardiogram, J. Clin. Invest. 16:799, 1937.
115. Eckstein, J. W., Hamilton, W. K., and McCammond, J. M.: The effect of thiopental on peripheral venous tone, Anesthesiology 22:525, 1961.
116. Shaw, W. M., Papper, E. M., and Rovenstine, E. A.: The influence of Dibenamine upon circulatory reactions to ephedrine and Neo-Synephrine in normal man, J. Lab. & Clin. Med. 34:669, 1949.
117. Maxwell, M. H., Morales, P., and Crowder, C. H., J.: Effect of therapeutic doses of ephedrine on renal clearances in normal man, Proc. Soc. Exper. Biol. & Med. 77:539, 1951.
118. Allen, W. J.: The action of adrenaline, ephedrine and Methedrine on the circulation in man, Clin. Sc. 6:269, 1948.
119. Chen, K. K., and Schmidt, C. F.: Ephedrine and related substances, Medicine 9:1, 1930.
120. Wegria, R.: Pharmacology of the coronary circulation, Pharmacol. Rev. 3:197, 1951.
121. Melville, K. I., and Lu, F. C.: Effects of ephedrine, phenylephrine, isopropylarterenol and methoxamine, on coronary flow and heart activity as recorded concurrently, Arch. internat. pharmacodyn. 92:108, 1952.
122. Churchill-Davidson, H. C., and Swan, H. J. C.: Noradrenaline and Methedrine—a comparison of their circulatory actions, Anaesthesia 7:4, 1952.
123. Churchill-Davidson, H. C., Wylie, W. D., Miles, B. E., and de Wardener, H. E.: The effects of adrenaline, noradrenaline, and Methedrine on the renal circulation during anaesthesia, Lancet 2:803, 1951.
124. Eckstein, J. W., and Hamilton, W. K.: Effects of sympathomimetic amines on forearm venous distensibility, pressure and volume, Circulation 16:873, 1957.
125. Keys, A., and Violante, A.: The cardiocirculatory effects in man of Neo-Synephrine (1-α-hydroxy-β-methylamino-3-hydroxy-ethylbenzene hydrochloride), J. Clin. Invest. 21:1, 1942.
126. Horvath, S. M., and Knapp, D. W.: Hemodynamic effects of Neo-Synephrine, Am. J. Physiol. 178:387, 1954.
127. Youmans, W. B., Haney, H. F., and Aumann, K. W.: Relation of the groups of the adrenaline molecule to its cardioaccelerator action, Am. J. Physiol. 130:190, 1940.
128. Youmans, W. B., Goodman, M. J., and Gould, J.: Neo-Synephrine in treatment of paroxysmal supraventricular tachycardia, Am. Heart J. 37:359, 1949.
129. Crosley, A. P., Jr., Clark, J. K., and Barker, H. G.: The renal hemodynamic effects of phenylephrine (Neo-Synephrine) hydrochloride in man, J. Pharmacol. & Exper. Therap. 101:153, 1951.
130. Mills, L. C., and Moyer, J. H.: Methoxamine effect on blood pressure and renal hemodynamics, Am. J. M. Sc. 233:409, 1957.
131. Nathanson, M. H., and Miller, H.: Clinical observations on a new epinephrine-like compound methoxamine, Am. J. M. Sc. 223:270, 1952.
132. Aviado, D. M., Jr., and Wnuck, A. L.: Mechanisms for cardiac slowing by methoxamine, J. Pharmacol. & Exper. Therap. 119:99, 1957.
133. Brewster, W. R., Jr., Osgood, P. F., Isaacs, J. P., and Goldberg, L. I.: Hemodynamic effects of a pressor amine (methoxamine) with predominant vasoconstrictor activity, Circulation Res. 8:980, 1960.
134. Horsely, A. W., and Eckstein, J. W.: Unpublished observations.
135. West, J. W., and Aviado, D. M., Jr.: Cardiac effects of methoxamine, with special reference to intracoronary injection, Am. J. M. Sc. 231:599, 1956.
136. Gilbert, J. L., Lange, G., Palevos, I., and Brooks, C. McC.: Effects of vasoconstrictor agents on cardiac irritability, J. Pharmacol. & Exper. Therap. 123:9, 1958.
137. Moyer, J. H., Huggins, R. A., Handley, C. A., and Mills, L. C.: Effect of hexamethonium chloride on cardiovascular and renal hemodynamics and on electrolyte excretion, J. Pharmacol. & Exper. Therap. 106:157, 1952.
138. Grob, D., Scarborough, W. R., Kattus, A. A., J., and Langford, H. G.: Further observations on the effects of autonomic blocking agents in patients with hypertension. II. Hemodynamic ballistocardiographic and electrocardiographic effects of hexamethonium and pentamethonium, Circulation 8:352, 1953.
139. Freis, E. D., Rose, J. C., Partenope, E. A., Higgins, T. F., Kelly, R. T., Schnaper, H. W., and Johnson, R. L.: The hemodynamic effects of hypotensive drugs in man. III. Hexamethonium, J. Clin. Invest. 32:1285, 1953.
140. Crumpton, C. W., Rowe, G. G., O'Brien, G., and Murphy, Q. R., Jr.: The effect of hexamethonium bromide upon coronary flow cardiac work and cardiac efficiency in normotensive and renal hypertensive dogs, Circulation Res. 2:79, 1954.
141. Pugh, L. G. C., and Wyndham, C. L.: The circulatory effects of high spinal anaesthesia in hypertensive and control subjects, Clin. Sc. 9:189, 1950.
142. Sancetta, S. M., Lynn, B., Simeone, F. A., and Scott, R. W.: Studies of hemodynamic

changes in humans following induction of low and high spinal anesthesia. I. General considerations of the problem. The changes in cardiac output, brachial arterial pressure, peripheral and pulmonary oxygen contents and peripheral blood flow induced by spinal anesthesia in humans not undergoing surgery. Circulation 6:339, 1952.

143. White, J. C., and Smithwick, R.: The autonomic nervous system, ed. 2, New York, 1947, The Macmillan Company.

144. Adriani, J., and Rovenstine, E. A.: Effects of spinal anesthesia upon venous pressure in man, Proc. Soc. Exper. Biol. & Med. 45:415, 1940.

145. Hellerstein, H. K., Brofman, B. L., and Caskey, W. H.: Shock accompanying myocardial infarction: treatment with pressor amines, Am. Heart J. 44:407, 1952.

146. Sampson, J. J., and Zipser, A.: Norepinephrine in shock following myocardial infarction. Influence upon survival rate and renal function, Circulation 9:38, 1954.

147. Sampson, J. J.: Shock of cardiac origin, Mod. Concepts Cardiovas. Dis. 26:379, 1957.

148. Selzer, A., and Rytand, D. A.: Use of drugs in shock accompanying myocardial infarction, J.A.M.A. 168:762, 1958.

149. Friedberg, C. K.: Cardiogenic shock in acute myocardial infarction, Circulation 23:325, 1961.

150. Miller, A. J., Shifrin, A., Kaplan, B. M., Gold, H., Billings, A., and Katz, L. N.: Arterenol in treatment of shock, J.A.M.A. 152:1198, 1953.

151. Freis, E. D., Schnaper, H. W., Johnson, R. L., and Schreiner, G. E.: Hemodynamic alterations in acute myocardial infarction. I. Cardiac output, mean arterial pressure, total peripheral resistance, "central" and total blood volumes, venous pressure and average circulation time, J. Clin. Invest. 31:131, 1952.

152. Sarnoff, S. J., Case, R. B., Berglund, E., and Sarnoff, L. C.: Ventricular function. V. The circulatory effects of Aramine: mechanism of action of "vasopressor" drugs in cardiogenic shock, Circulation 10:84, 1954.

153. Gazes, P. C., Goldberg, L. I., and Darby, T. D.: Heart force effects of sympathomimetic amines as a basis for their use in shock accompanying myocardial infarction, Circulation 8:883, 1953.

154. MacLean, L. D., and Weil, M. H.: Hypotension (shock) in dogs produced by Escherichia coli endotoxin, Circulation Res. 4:546, 1956.

155. Weil, M. H., MacLean, L. D., Visscher, M. B., and Spink, W. W.: Studies on the circulatory changes in the dog produced by endotoxin from gram-negative microorganisms, J. Clin. Invest. 35:1191, 1956.

156. Zimmerman, B., and Beck, L.: Effect of endotoxin on cardiac output and reflex dilatation in the anesthetized dog, Fed. Proc. 19:88, 1960.

157. Gilbert, R. P.: Mechanism of the hemodynamic effect of endotoxin, Physiol. Rev. 40:245, 1960.

158. Spink, W. W.: The pathogenesis and management of shock due to infection, Arch. Int. Med. 106:433, 1960.

159. Altschule, M. D., Freedberg, A. S., and McManus, M. G.: Circulation and respiration during an episode of chill and fever in man, J. Clin. Invest. 24:878, 1945.

160. Altschule, M. D., and Freedberg, A. S.: Circulation and respiration in fever, Medicine 24:403, 1945.

161. Bradley, S. E., Chasis, H., Goldring, W., and Smith, H. W.: Hemodynamic alterations in normotensive and hypertensive subjects during the pyrogenic reaction, J. Clin. Invest. 24:749, 1945.

162. Entwhistle, G., and Hale, E.: Hemodynamic alterations in hemorrhagic fever, Circulation 15:414, 1957.

163. Weil, M. H., Hinshaw, L. B., Visscher, M. B., Spink, W. W., and MacLean, L. D.: Hemodynamic effects of vasopressor agent (metaraminol) on hypotension in dogs produced by endotoxin, Proc. Soc. Exper. Biol. & Med. 92:610, 1956.

164. Wise, R. I., Shaffer, J. M., and Spink, W. W.: The syndrome of vascular collapse due to gram-negative bacteria: its management, l-norepinephrine and antibiotics, J. Lab. & Clin. Med. 40:961, 1952.

165. Weil, M. H.: Clinical studies on a vasopressor agent: metaraminol. II. Observations on its use in the management of shock, Am. J. M. Sc. 230:357, 1955.

166. Hall, W. H., and Gold, D.: Shock associated with bacteremia, Arch. Int. Med. 96:403, 1955.

167. Thomas, L.: The role of epinephrine in the reactions produced by the endotoxin of gram-negative bacteria. I. Hemorrhagic necrosis produced by epinephrine in the skin of endotoxin-treated rabbits, J. Exper. Med. 104:865, 1956.

168. Zweifach, B. W., Nagler, A. L., and Thomas, L.: The role of epinephrine in the reactions produced by the endotoxin of gram-negative bacteria. II. The changes produced by endotoxin in the vascular reactivity to epinephrine in the rat mesoappendix and the isolated, perfused rabbit ear, J. Exper. Med. 104:881, 1956.

169. Thomas, L., Zweifach, B. W., and Benacerraf, B.: Mechanisms in the production of tissue damage and shock of endotoxins, Tr. A. Am. Physicians 70:54, 1957.

170. Corday, E., and Williams, J. H., Jr.: Effect of shock and of vasopressor drugs on the regional circulation of the brain, heart, kidney and liver, Am. J. Med. 29:228, 1960.

171. Gilmore, J. P., Smythe, C. M., and Handford, S. W.: The effect of l-norepinephrine on cardiac output in the anesthetized dog during graded hemorrhage, J. Clin. Invest. 33:884, 1954.

172. Lansing, A. M., and Stevenson, J. A. F.: Mechanism of action of norepinephrine in hemorrhagic shock, Am. J. Physiol. 193:289, 1958.

173. Shorr, E., Zweifach, B. W., Furchgott, R. F., and Baez, S.: Hepatorenal factors in circula

tory homeostasis. IV. Tissue origins of the vasotropic principles VEM and VDM which appear during evolution of hemorrhagic and tourniquet shock, Circulation 3:42 1951

174 Zweifach, B W., and Thomas L. The relationship between the vascular manifestations of shock produced by endotoxin, trauma, and hemorrhage. I. Certain similarities between the reactions in normal and endotoxin tolerant rats, J Exper Med. 106:385 1957

175. Nathanson, M H and Miller H The action of norepinephrine, epinephrine and isopropyl norepinephrine on the rhythmic function of the heart, Circulation 6:238, 1952.

176. McGinn, J T and Schluger J Levarterenol bitartrate (Levophed) in treatment of cardiac arrhythmias, Am Heart J 50:635 1955

177 Donegan, C. K., and Townsend, C. V Phenylephrine hydrochloride in paroxysmal supraventricular tachycardia J A.M.A. 157:716 1955

178 Gold, H., and Corday E. Vasopressor therapy in the cardiac arrhythmias, New England J Med. 260 1151 1959

179 Corday E., Williams, J H DeVera L. B and Gold, H Hemodynamics of the coronary circulation during cardiac arrhythmias, Mod. Concepts Cardiovas. Dis. 27:493 1958.

180. Corday E., Gold, H deVera, L.B Williams J H., and Fields J Effect of the cardiac arrhythmias on the coronary circulation Ann Int. Med. 50:535 1959

181 Lever A. F Mowbray J F and Peart, W S. Blood flow and pressure after noradrenaline infusion, J Physiol 146:43P 1959

182. Blacket, R. B Pickering, G W and Wilson, G. M The effects of prolonged infusions of noradrenaline and adrenaline on the arterial pressure of the rabbit, Clin. Sc. 9:247 1950

183 Duner H and Euler U. S. von Secondary fall in blood pressure following noradrenaline infusion in the cat, Acta physiol scandinav 38:355 1957

184 Lundberg, A. Adrenaline and transmission in the sympathetic ganglion of the cat, Acta physiol. scandinav 26:252, 1952

185 Swan, H. J C. Observations on a central dilator action of adrenaline in man, J Physiol 112:426, 1951

186. B omage P R Vasopresso Canad Anaesth Soc. J :310 1960

187 Burget, G E., and Visscher M B Variations of the pH of the blood and the response of the vascular system to adrenaline Am. J Physiol. 81 113 1927

188 Surtshin, A., Rodbard, S and Katz, L. N Inhibition of epinephrine action in severe hypoxemia Am J Physiol. 152:623 1948

189 Campbell, G S Houle, D B Crisp N W J., Weil, M H and Brown, E. B Jr Depressed response to intravenous sympathicomimetic agents in humans during acidosis Dis. Chest 33 18, 1958.

190 Duner H., and Euler U. S. von Effect of reduced ventilation on systemic blood pressure and blood flow in the hind part of the cat during infusion of noradrenaline, Acta physiol. scandinav 46:201 1959

191 Darby T D Aldinger E. E., Gadsden, R. H and Thrower W B Effects of metabolic acidosis on ventricular isometric systolic tension and the response to epinephrine and levarterenol, Circulation Res 8:1242, 1960

192. Weil, M H Houle, D B Brown, F B Jr Campbell, G S., and Heath, C Vasopressor agents—influence of acidosis on cardiac and vascular responsiveness California Med 88:437 1958.

193 Eckman P L., Brunson, J G and Campbell J B Increasing incidence of liver necrosis possible relationship to administration of vasopressor amines, Circulation 16:874 1957

194 Boughton, G A., and Sommers, S C Renal changes in shock treated with levarterenol (Levophed) Am. J Clin. Path. 27:29 1957

195. Greenbaum D Gangrene of the extremities following cardiac infarction and noradrenaline therapy Lancet 1 1103 1958

196 Szakacs, J E., and Cannon A. l-Norepinephrine myocarditis, Am J Clin. Path. 30:425 1958.

197 Zucker G Use of phentolamine to prevent necrosis due to levarterenol, J.A.M A. 163 1477 1957

198. Zucker G Eisinger R. P Flock, M H., and Singer M M Treatment of shock and prevention of ischemic necrosis with levarterenol phentolamine mixtures, Circulation 22:935 1960

199 Sampson, J J and Griffith, G C. Norepinephrine in the treatment of the elderly patient, Geriatrics 11:60 1956

200 Pelner L., Waldman, S., and Rhoades, M G The problem of levarterenol (Levophed) extravasation an experimental study Am. J M. Sc 236 755 1958.

201 Fine, J Fischmann, J and Frank, H. A. The effect of adrenal cortical hormones in hemorrhage and shock, Surgery 12 1 1942

202. Hmanga, K. A., Brofman, B L and Wiggers, C J Ineffectiveness of adrenocortical preparations in standardized hemorrhagic shock, Proc Soc Exper Biol & Med. 52 77 1943

203 Swingle W W Overman, R. R Remington J W Kleinberg W and Eversole W J Ineffectiveness of adrenal cortex preparations in the treatment of experimental shock in nonadrenalectomized dogs, Am J Physiol 139:481 1943

204. Howard J M and DeBakey M E The treatment of hemorrhagic shock with cortisone and vitamin B_{12} Surgery 30 161 1951

205. Frank, H A Jacob S Weizel, H A E. Reiner L Cohen, R and Fine, J Effects of ACTH and cortisone in experimental hemorrhagic shock, Am J Physiol. 180:282 1955

206 Lansing A. M Stevenson, J A F and Gowdey C W The effect of noradrenaline on the survival of rats subjected to hemorrhagic shock, Canad. J Biochem. & Physiol 35:93 1957

207 Spink, W W., and Vick, J Evaluation of plasma, metaraminol, and hydrocortisone in experimental endotoxin shock, Circulation Res. 9 184, 1961

Annotations

Objective evaluation of ischemic heart disease

The urgent need for a practical, safe, and objective means of evaluating patients who are thought to have ischemic heart disease is acknowledged generally. In cases in which the objective changes of myocardial infarction have not occurred, careful analysis of the historical facts remains the primary means of diagnosing this disorder.

The inadequacies of present instrumental methods can be summarized briefly by reviewing the highlights of the experiences of our laboratory which used conventional equipment in a long-range study of normal subjects and patients with clinical ischemic heart disease (viz., either documented myocardial infarction or typical angina pectoris). The electrocardiogram *which is taken while the patient is* resting is abnormal in 25 per cent of the patients with angina pectoris, and the changes are usually nonspecific. The two-step exercise test, when judged by Master criteria, is positive in 50 per cent of the patients with angina pectoris or remote myocardial infarction but falsely positive in 25 per cent of the normal control subjects. Other stress procedures for electrocardiographic studies have not proved of value in our experience. The high-frequency ballistocardiogram is abnormal in 75 per cent of the patients with angina pectoris but also abnormal in 25 per cent of the normal subjects, especially when the subjects are in the late years of life. Normal persons under 40 years of age have normal ballistocardiograms, but a rapid increase in incidence of abnormality occurs in subsequent decades. More refined ballistocardiographic techniques have, as yet, failed to discriminate further the normal from the diseased groups. The ballistocardiographic cigarette test is positive in almost 50 per cent of the patients with ischemic heart disease, in contrast with less than 10 per cent of control subjects. Levels of lipid in serum are of statistical value, but are not *in themselves diagnostic in individual* patients.

Despite many unanswered problems in regard to the correlation of the gross anatomic state of the coronary arteries and the physiologic state of the myocardium, it is of considerable interest to correlate the findings obtained by means of conventional laboratory instruments with those obtained in the same patients by means of coronary arteriography. A small group of patients so studied has been assembled, and the highlights of these largely preliminary observations deserve consideration. Thirty-five patients (who were surveyed for possible coronary artery operation, or because of severe pain which was thought possibly to be due to ischemia) have had arteriograms, largely with the "flush" technique, and most were recorded on biplane static radiographs.[1] A few had cinearteriograms. Since a larger number of subjects is now under investigation by more refined arteriographic methods, only the outstanding observations seem worthy of comment.

The electrocardiogram was abnormal in 60 per cent of the patients whose arteriograms demonstrated widespread and severe atherosclerosis, and usually normal when the structural changes were less severe. Three of the 6 subjects who had normal arteries (by this method) had abnormal electrocardiograms. The two-step test was positive in approximately one half of the patients with only moderate atheromatous lesions, but also positive (0.5 mm. S-T depression) in almost one half of those with normal arteriograms. If more rigid criteria were adopted (1.5 mm. ischemic depression after exercise), there were no positive tests in patients with normal arteriograms and the only positive tests were in patients with the most severe obstructive lesions. Both the resting ballistocardiogram and the BCG cigarette test were abnormal in only one half of the patients whose arteriograms showed significant atherosclerosis.

These observations, although in a small group of subjects, emphasize that, when any one of our conventional laboratory instruments is applied to the study of subjects with chest pain, only limited information can be obtained. When the resting and postexercise electrocardiogram and the resting and postsmoking ballistocardiogram are combined, 25 per cent of the patients with arteriographic evidence of atherosclerosis are not detected by these instruments. The high incidence of abnormal laboratory findings in subjects with normal arteriograms likewise leads to speculation in regard to the significance of possible vascular lability and "functional" myocardial aberration or *the possibility that certain* patients have anginal pain on the basis of nonvascular (and nonvalvular) heart disease and might be recognized more readily when arteriography is more widely applied.

At present it would seem that objective confirmation of the diagnosis of ischemic heart disease is achieved when (a) electrocardiographic changes occur during spontaneous episodes of chest pain and (b) the exercise test results in ischemic S-T segment depression of 1.5 mm. or more. *Ancillary* support is obtained in younger subjects whose ballistocardiograms are abnormal and whose cigarette tests are positive.

Coronary arteriography would seem to be a sig-

nificant addition to the diagnostic armamentarium. It shows great promise as a method of investigation, and should increase considerably our knowledge of the coronary arterial system. Visualization of the coronary arteries is a necessity when direct operation on the coronary arteries is under consideration. Arteriographic evaluation of patients with doubtful diagnoses should not be considered as a routine procedure, but if the clinical need for a definitive decision is sufficiently compelling, this technique can be utilized when other means of objective analysis have failed.

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REFERENCES

1. Scarborough, W. R., Mason, R. E., Davis, F. W., Singewald, M. L., Baker, B. M., and Lore, S. A.: A ballistocardiographic and electrocardiographic study of 328 patients with coronary artery disease: comparison with results from a similar study of apparently normal persons, AM. HEART J. 44:645, 1952.
2. Master, A. M., Nuzie, S., Brown, R. C., and Parker, R. C.: The electrocardiogram and the "two-step" exercise. A test of cardiac function and coronary insufficiency, Am. J. M. Sc. 207:435, 1944.
3. Davis, F. W., Scarborough, W. R., Mason, R. E., Singewald, M. L., and Baker, B. M.: The effects of exercise and smoking on the electrocardiograms and ballistocardiograms of normal subjects and patients with coronary artery disease, AM. HEART J. 46:529, 1953.
4. Scarborough, W. R., Davis, F. W., Baker, B. M., Mason, R. E., Singewald, M. L., Lore, S. A., and Fox, L. M.: A ballistocardiographic study of 369 apparently normal persons, AM. HEART J. 45:161, 1953.
5. Davis, F. W.: The role of the ballistocardiograph in the diagnosis and management of patients with coronary heart disease, Am. J. Cardiol. 3:103, 1959.
6. Davis, F. W., Scarborough, W. R., Mason, R. E., Singewald, M. L., and Baker, B. M.: The ballistocardiographic cigarette test: further observations, AM. HEART J. 51:165, 1956.
7. Lang, E. K., and Sabiston, D. C., Jr.: Coronary arteriography in the selection of patients for surgery, Radiology 76:32, 1961.
8. Ross, R. S.: Personal communication.

Adult rheumatic fever

Acute rheumatic fever is generally considered to be a disease of childhood, and the peak incidence of the disease is in the 10 to 14-year-old age group. Adults, however, are also susceptible, but the diagnosis of acute rheumatic fever is often more difficult for three reasons: (1) because of similarities to other polyarthritides which are common in the adult, such as early rheumatoid arthritis, systemic lupus erythematosus, and gout, (2) because major manifestations, such as chorea, erythema marginatum, and subcutaneous nodules, are less frequent in the adult, and (3) because in the patient with previous rheumatic heart disease the diagnosis of carditis may be more difficult to establish. The mere presence of heart murmurs, as well as of various nonspecific findings, such as fever, increased erythrocyte sedimentation rate, the appearance of acute-phase reactants, and electrocardiographic abnormalities, may indicate complications of rheumatic heart disease other than recrudescence of activity. Finally, since acute rheumatic fever is generally considered to be a disease of childhood, the physician often fails to consider it seriously in the differential diagnosis in the older age groups.

A series of 30 patients, 30 to 59 years of age, were studied. Fourteen of these were seen in what appeared to be the initial attack of rheumatic fever, although prior subclinical rheumatic fever could not be excluded. The experience in this group was consistent with the established view that antecedent streptococcal infection was as important in the development of acute rheumatic fever in the adult as in the child. Symptoms and findings referable to the joints were most common, and as in the classic description of acute rheumatic fever, the arthritis was most often migratory, with involvement of multiple joints. The large joints of the lower extremities were most often affected, sometimes with frank effusion. However, biarticular rheumatism did occur, and in many instances the typical nature and distribution of the manifestations in the joints necessitated appropriate testing for exclusion of other forms of arthritis. The incidence of acute carditis was more difficult to determine because many patients who had had rheumatic heart disease were included. The mere presence of murmurs obviously did not establish a diagnosis of active rheumatic carditis. Likewise, a fixed arrhythmia or the presence of cardiac enlargement did not help in the diagnosis. When the modified Jones criteria[1] were used, it was concluded that active carditis was present in 10 patients. Two additional patients did not fulfill these rigid clinical criteria, but, at necropsy, were found to have widespread, unequivocally active rheumatic endocarditis and myocarditis. Two additional patients were included in this group because of the appearance of congestive heart failure for the first time in association with acute rheumatic polyarthritis.

The considerably greater incidence of arthritis,

as compared with carditis, in adult rheumatic fever deserves emphasis since rheumatic fever is quite often mistakenly excluded from the differential diagnosis of a polyarthritis when evidence of cardiac involvement is lacking. It should be borne in mind that the relative incidence of these two major manifestations is distinctly related to the age group under study. Bland and Jones[3] found carditis to be more prevalent than arthritis in persons with rheumatic fever who were under the age of 21 years, and similar findings were noted in the United Kingdom–United States study[4] which was concerned with patients under 16 years of age. On the other hand, when a series included young adults[6] or excluded children entirely, arthritis appeared to be the more common manifestation.

No statement is possible concerning the incidence of valvular damage after the attack of acute rheumatic fever in adult patients. The incidence of acute carditis in the adult appears to be lower than in the child and it is possible that the incidence of valvular disease also may be lower in the adult group. No acceptable data on this point are yet available.

In summary, rheumatic fever in the adult differs from rheumatic fever in the child in the higher incidence of arthritis as compared with carditis, and the extremely low incidence of subcutaneous nodules, chorea, and erythema marginatum.

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REFERENCES

1. Pader, E., and Elster, S. K.: Studies of acute rheumatic fever in the adult. I. Clinical and laboratory manifestations in thirty patients, Am. J. Med. 26:424, 1959.
2. American Heart Association. Report of the Committee on Standards and Criteria for Programs of Care of the Council of Rheumatic Fever: Jones criteria (modified) for guidance in the diagnosis of rheumatic fever, Mod. Concepts Cardiovas. Dis. 24:291, 1955.
3. Bland, E. F., and Jones, T. D.: Rheumatic fever and rheumatic heart disease. A twenty year report on 1,000 patients followed since childhood, Circulation 4:836, 1951.
4. United Kingdom United States Joint Report on Rheumatic Fever: The treatment of acute rheumatic fever in children. A cooperative clinical trial of ACTH, cortisone and aspirin, Circulation 11:343, 1955.
5. Lieber, S. L., and Holoubek, J. E.: Acute rheumatic fever in a large southern hospital over the five year period 1950 through 1954, Ann. Int. Med. 44:118, 1956.
6. Joos, H. A., and Katsampes, C. P.: A community study of rheumatic fever, A.M.A. J. Dis. Child. 83:37, 1952.
7. Bruce, R. A.: Current status of acute rheumatic fever in the state of Washington, Northwest Med. 52:636, 1953.

The vasa vasorum in coronary atherosclerosis

Atherosclerosis, especially coronary atherosclerosis, is perhaps the most important disease with which modern Western man contends. Despite this, it is still beyond our ability to diagnose its presence, much less its extent, or to influence its course with any confidence. Though experience at postmortem examination indicates that the disease is present to some extent in all adults, its existence is not associated with any clinical manifestations in most instances. The first indication of its presence is usually the sudden appearance of a complication—critical stenosis of an artery. Such an acute complication need not mean *that a thrombus has formed, but it* does mean that something has happened abruptly. If there has been no precipitous increase in demand for blood, there must have been a sudden diminution of the cross-sectional area, and thrombosis is far and away the most likely basis for this. Hematomatous enlargement of a plaque, embolism, and other mechanisms are responsible for a very small per cent of the occlusions. Granted that if there were no atheromatosis there would be no complications of it, the pragmatic and immediate problem is what causes the complications rather than what causes the underlying (asymptomatic) disease. Efforts to understand these developments have been concerned primarily with studies of the mechanism of clotting and attempts to prevent them have centered around anticoagulants of various sorts. Progress has been made in the study of these aspects of the problem, but little if any unequivocal benefit has accrued to patients who are suffering from infarction of the brain or myocardium. Meanwhile, very little attention has been directed to other factors which might provide a basis for treatment—*the disease in the* wall of the artery itself.

Why does a thrombus form at a given point in an artery and at a given point in time? *To say that* atherosclerosis is the cause is no answer, since the atheroma concerned has been present for a long time. It is possible that something happened in that atheroma, though, that served as a *precipitating factor. Addressing himself to this question in 1936,* Dr. J. C. Paterson[1] studied the lesions by a tedious and demanding serial-section technique and emphasized the little-recognized fact that atheromata are vascularized masses of tissue "like other 'omas,'" and, like them, subject to vascular accidents. He observed that subjacent to thrombi which overlie atheromata are hemorrhages in the substance of the

atheroma. It was his hypothesis that the process of thrombosis represented largely a natural reaction to injury of the endothelium of the intima overlying the atheroma. Some occlusions were shown to be the result of hematomatous enlargement of the plaques in the absence of the formation of thrombus.

Studies designed to observe these phenomena[1-4] have all supported the view that such might be important. These studies are exceptionally tedious, not suitable for routine application to autopsy material, and rarely done. They have emphasized, though, that the coronary artery is not an inert polyethylene tube, but a complicated organ subject to disease of its blood supply just like other organs. By the same token that the coronary artery is important to the economy of the organism, the blood supply of the coronary artery is important and deserves more investigation. One of the dangers of the widespread complacent use of anticoagulants in the management of symptomatic coronary atherosclerosis is that it may stifle the investigation of other approaches to the problem.

Attention directed to measures which would diminish the propensity to intra-atheromatous hemorrhage might result in fewer catastrophic acute occlusive complications of atherosclerosis.

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REFERENCES

1. Paterson, J. C.: Vascularization and hemorrhage of the intima in arteriosclerotic coronary arteries, Arch. Path. 22:313, 1936.
2. Winternitz, M. C., Thomas, R. M., and Lecompte, P. M.: The biology of arteriosclerosis, Springfield, Ill., 1938, Charles C Thomas, Publisher.
3. Wartman, W. B.: Occlusion of the coronary arteries by hemorrhage into their walls, Am. Heart J. 15:459, 1938.
4. Morgan, A. D.: The pathogenesis of coronary occlusion, Springfield, Ill., 1956, Charles C Thomas, Publisher.

The etiology of digital clubbing

Digital clubbing, which occurs in a number of different diseases, remains one of the partially unexplained states in medicine. Hippocrates has been credited with the first description of the increase in volume of the finger tip as the important feature in clubbing. One author even referred to clubbing as "The Hippocratic Fingers."[1] Actually, it was Caelius Aurelianus, in 200 A.D., who first drew attention to the features of digital clubbing in chronic diseases. Apparently there was little interest in the subject until Pigeaux[2] published the first definitive work on clubbing in 1832. Bamberger in 1889 and 1891 and Marie, in 1890 first described the syndrome of hypertrophic pulmonary osteoarthropathy. Since that time numerous writings on the possible etiology of digital clubbing have appeared in the literature.

Pigeaux's[2] description of clubbing in 1832, attributed the phenomenon to the formation of blood tinged fluid in the soft tissue beneath the nail. Grafe and Schneider in 1913 first concluded that the abnormal curvature of the nail was due to increased thickness of the nail bed. Schirmer[4] in 1923 reported that fine connective tissue fibrils in a homogeneous basophilic ground substance which contain many capillaries and a few round cells are the main constituents of the thickened subcutaneous tissue of the nail bed. In 1924 Campbell[5] compared a clubbed finger accidentally removed during life with a normal finger and concluded that edema of the nail bed was the cause of clubbing; however he was unable to give any explanation for the edema or passive congestion. Bigler[5,6] described coils of arteriovenous anastomoses in sagittal section of clubbed thumbs. The nail beds were thickened also with primitive fibroblasts and round cells.

In 1937 Mendlowitz[6,7] reported the temperatures of fingers in 11 normal subjects and 11 subjects with unilateral clubbing and calculated the maximum elimination of heat from the finger tip. He concluded that the flow of blood per unit of surface area was greater in the clubbed finger tips than in the normal ones. In 1941 he[7,8] found that arterial blood pressure and blood flow in the digits were also increased in clubbed digits, except in those of familial variety. Wilson in 1959 confirmed Mendlowitz's findings of increased blood flow in the finger tips of these subjects and noted that clubbing on the left hand regressed after ligation of the left subclavian artery in patients with the tetralogy of Fallot who were operated upon by the Blalock technique. He also concluded that the increased flow of blood to clubbed digits is considered to be in excess of physiologic requirements and passes largely through numerous arteriovenous anastomoses in the distal segments. This congestion of the venules with oxygenated blood under relatively high pressure

by ischemic skeletal muscle, spleen and liver and the material from the liver was identified as ferritin. Ferritin, in its reduced form, blocked the vasoconstrictive action of epinephrine, but in its oxidized form it was inert against epinephrine. Crismon and co-workers[13] reported from their studies on rabbits and rats that the flavonoid rutin given intravenously or orally blocked the vasodepressor effect of ferritin. Clark and Mackay had previously reported that rutin does not exert any specific chemical or therapeutic effect when administered orally but that it is destroyed at body temperature.

In 1959 Hall[15] postulated that clubbing was caused by the presence in peripheral blood of a *substance normally inactivated by the lungs* which dilated the small vascular shunts. He suggested that this substance might be ferritin. On the bases of the reported findings on ferritin and rutin he *performed a study on 8 subjects with clubbing and* on 8 subjects without clubbing. The capillary blood flow through the finger tips was evaluated by a clearance technique utilizing radiosodium (Na^{24}) which was described by Kety.[16] Radiosodium (Na^{24}) was injected 2 to 3 mm. proximal to the nail fold of the middle finger and when 50 per cent activity had disappeared 50 mg. of rutin in 10 c.c. of normal saline was injected intravenously into the opposite arm within 20 to 30 seconds. There was a notable increase in the slope of the absorption curve in subjects with clubbing. This revealed that the rate *of absorption of radiosodium from clubbed fingers* was much slower than from normal fingers, and the rate increased after rutin was administered. Hall concluded from these findings that digital clubbing may be the long-term result of dilatation of arteriovenous anastomoses in the nail beds by reduced ferritin which had evaded oxidation.

Mendlowitz has confirmed the basic concept of what happens in digital clubbing by a demonstration of the ability of arteriovenous fistulas to open in the terminal digit. Hall's concept may be reasonable in cases of clubbing in which obvious right-to-left shunts or pulmonary diffusion defects exist, but it hardly seems feasible when clubbing occurs unilaterally or when no such cardiac shunt or pulmonary diffusion defects are detectable. A review of the literature on rutin and its effect on vasodepressor materials (VDM), such as ferritin, shows that there is controversial evidence on the action of rutin. No reports were found on the comparison of the amount of reduced ferritin as opposed to oxidized ferritin in subjects with clubbing and in normal subjects. Hall's work is stimulating but needs confirmation, because digital clubbing may have multiple causes.

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REFERENCES

1. Hippocrates: The book of prognostics, *in* The genuine works of Hippocrates, translated by F. Adams, London, 1849, The Sydenham Society, Vol. I, p. 249.
2. Campbell, D.: The Hippocratic fingers, Brit. M. J. 1:145, 1924.
3. *Caelius Aurelianus*: On chronic diseases, *in* Drabkin, I. E.: On acute diseases and on chronic diseases, Chicago, 1950, University of Chicago Press, Book 2, Section 14, p. 679.
4. Bigler, F. C.: The morphology of clubbing, Am. J. Path. 34:237, 1958.
5. Mendlowitz, M.: Some observations on clubbed fingers, Clin. Sc. 3:387, 1937-38.
6. Dorney, E. R., et al: Unilateral clubbing of the fingers due to absence of the aortic arch, Am. J. Med. 18:150, 1955.
7. Mendlowitz, M.: Measurements of blood flow and blood pressure in clubbed fingers, J. Clin. Invest. 20:113, 1941.
8. Mendlowitz, M.: The digital circulation, Am. Heart J. 57:309, 1959.
9. Wilson, G. M.: Local circulatory changes associated with clubbing of the fingers and toes, Quart. J. Med. 21:201, 1959.
10. Bigler, F. C.: The morphology of clubbing, *Circulation 19:312, 1959.*
11. Shorr, E.: Intermediary and biological activities of ferritin, Harvey Lectures 50:112, 1954.
12. Granick, S.: Structure and physiological functions of ferritin, Physiol. Rev. 31:489, 1951.
13. Crismon, et al: Rutin and other flavonoids as potentiators of terminal vascular responses to epinephrine and as antagonists of vasodepressor materials, Am. J. Physiol. 164:391, 1951.
14. Clark, W. G., and Mackay, E. M.: The absorption and excretion of rutin and related flavonoid substances, J.A.M.A. 143:1411, 1950.
15. *Hall, G. H.: The cause of digital clubbing*, Lancet 1:750, 1959.
16. Kety, S. S.: Quantitative measurement of regional circulation by the clearance of radioactive sodium, Am. J. M. Sc. 215:352, 1948.

Book reviews

STRESS AND YOUR HEART. By Fred Kerner with an Introduction by Hans Selye, M.D. New York, 1961, Hawthorn Books, Inc. 237 pages. Price $4.95.

Here, with the clear sanction of its protagonist, is a restatement for the layman of the adaptation syndrome. The author in his version of how knowledge of the stress concept may be utilized to prevent the tension of everyday living from damaging the heart, outdoes the enthusiasm even of Selye. The style is fluent and engaging but the writing is loose and replete with overstatement. The author admits but discounts the role of heredity and diet in the causation of heart disease, baldly stating that "in pursuing his researches for more than a generation, Dr. Selye indicated quite clearly that stress is the true origin of degenerative disease," a conclusion which is, at best, premature. Furthermore, he assumes that the myocardial necroses of experimental animals are identical with spontaneous myocardial infarction of man, which likewise is an unproved assumption. His suggestions are well taken that we should recognize and not try to exceed our limitations, that we should avoid unnecessary haste, and that we should get enough sleep, exercise, and recreation. This is sound mental hygiene. But one could doubt the practicality if not the effectiveness of some of the measures recommended to dispel tension. This reviewer feels that to sift out fact from opinion in this work would require a discrimination possessed by very few nonmedical readers.

MECHANISMS OF DISEASE. By Ruy Perez Tamayo, M.D., Professor and Director, Department of Pathology, School of Medicine, National University of Mexico. Philadelphia, 1961, W. B. Saunders Company. 512 pages. Price $14.

This volume presents *general* aspects of disease mechanisms and is designed as a guide during the first stage of the study of pathology. It is divided into two parts. The first part is concerned with the fundamental principles of cellular pathology including chapters on degeneration, inflammation, transplantation, growth, differentiation, and the general pathology of tumors. The second part presents five general aspects of altered homeostasis, designated as the general pathology of connective tissues, host-parasite relations, immune response, body fluids and electrolytes, and metabolism and nutrition. Specific diseases are mentioned only to amplify the central theme. Frequent delightful quotations from the original writings of pioneers in medicine are blended into each topic. The section on chemotherapy contributed by Luis F. Bojalil, Q.B.P. is a definite asset to the chapter "General Pathology of Host-Parasite Relationship." The unique value of the book lies in its concise integration of cellular pathology and concepts of disease with a wide range of sciences, including immunochemistry, biochemistry, biophysics, biology, and clinical medicine. The bibliography shows a wide variety of authoritative publications, ranging from biochemical to clinical works. Occasional typographic errors are obvious and perhaps, more frequent than usually encountered. Rare misinterpretations of original publications are noted. The author's style of writing is smooth flowing and readable characterized by brevity and organization. In summary, the author presents a commendable synthesis of general disease processes in a concise, well-illustrated readable form which is of immeasurable supplementary value to the student, the teacher and the practicing physician who wishes to do more than diagnose and treat.

OXYTOCIN. Proceedings of an International Symposium held in Montevideo, 1959. Edited by R. Caldeyro-Barcia, Facultad de Medicina, Montevideo, and H. Heller, The University, Bristol. New York, 1961, Pergamon Press, Inc. 443 pages. Price $15.

This book represents the proceedings of an international symposium on oxytocin held in Montevideo during 1959. It includes many papers grouped according to the subjects discussed, namely "General Physiology and Pharmacology of Oxytocin," "The Mechanism of the Uterine Action of Oxytocin," "Oxytocin and the Pregnant Human Uterus," "Pharmacology of Peptides Related to Oxytocin," "Comparison of the Uterine Action of Oxytocin With That of Other Oxytocic Substances," "Oxytocinase," and "The Determination of Oxytocic Substances in Blood."

It is not possible to summarize in review form the many papers presented. They represent much important work by the leaders in this field. The symposium, though dated now, contains much of the important fundamental data on oxytocin and is highly recommended to those who wish to know more about this interesting polypeptide. Pharmacologists, physiologists, and clinicians should find this book very useful.

THE MYOCARDIUM—ITS BIOCHEMISTRY AND BIOPHYSICS. By Alfred P. Fishman, M.D., guest editor. New York, 1961, American Heart Association. Price $2.50.

This symposium brings together recent advances in basic science toward the understanding of the myocardium. It is presented in five parts: I. Ultrastructure, II. Biochemistry, III. Hibernation in Animals, IV. Contractile Problems, and V. Electrophysiology. Contributions to the symposium are made by approximately 30 outstanding authorities. General discussions following the presentations are included.

All those concerned with the study of the heart and circulation should be familiar with the contents of this publication. It represents an interesting and instructive collection of information, but, obviously only selected topics can be covered from this broad field.

SYMPOSIUM ON FOETAL AND NEONATAL PHYSIOLOGY. British Medical Bulletin, Volume 17, Number 2, May 1961. Scientific Editor: Professor K. W. Cross. Chairman of the Planning Committee for the Symposium: Professor J. H. Burn. London, 1961, Medical Department, The British Council. Price $3.25.

This symposium is authoritative and will prove to be a valuable and ready source of reference information for practical as well as research application.

Contributions include such varied topics as protein transfer across fetal membranes, the ability of young mammals to withstand total lack of oxygen, and blood pressure in the newborn baby, to mention a few. Subjects of anatomic interest include the histology of the placenta and the inferior aortico-pulmonary glomus, a particularly nicely executed presentation. Respiration in the newborn, perinatal mineral metabolism, and neonatal pediatrics should be of special interest to the clinician.

Each contribution is preceded by a short outline and supported by pertinent and sufficient reference material. The articles are concise and authoritative. The photomicrographs and other illustrative material are well executed and adequately explained.

Announcements

SHARE YOUR JOURNALS. The United States Committee of The World Medical Association is sponsoring a project to send used medical journals to physicians in Asia. Specialty journals, such as the *American Heart Journal* are needed.

If you wish to participate in this doctor-to-doctor program, please write to The World Medical Association, United States Committee, 10 Columbus Circle, New York 19, N. Y., listing the journal(s) you wish to contribute.

A course on INTERNAL MEDICINE FOR INTERNISTS will be presented at the Center for Continuation Study, University of Minnesota, April 16 through 18, 1962.

For additional information in regard to this course, write to the Director, Department of Continuation Medical Education, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14, Minn.

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Editorial

Nicotinic acid therapy in coronary disease

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Although proof of causal relationship is lacking the circumstantial evidence which associates the concentration of serum cholesterol (or beta-lipoprotein) with atheromatous conditions is so strong that the lowering of the serum cholesterol has been widely accepted as a prophylactic measure at least worthy of rigorous clinical trial. Whether the reduction in the concentration of cholesterol in the serum will alter the prognosis of patients with coronary disease, and whether the degree of hypocholesterolemia that is likely to ameliorate arterial changes is a practicable or attainable goal remains unknown. Nevertheless, accumulating experimental evidence would tend to support rather than to oppose the belief that one is doing good rather than harm with most measures currently in use for this purpose. Certainly in coronary patients and in high risk subjects (those with a bad family history, those with hypercholesterolemia, or those who are obese or hypertensive) in whom high values of serum cholesterol are observed it would seem prudent and justifiable to adopt some programme directed among other things toward reducing the level of cholesterol in the blood.

Dietary modification would undoubtedly be an initial consideration particularly in respect of quantity and quality of intake of fat. However experienced physicians have become increasingly aware of some of the difficulties pursuant to the introduction of dietary regimens, namely resistance by the patient, variability of responsiveness, and the necessity for the most rigid restriction if any impressive hypocholesterolemic effect is to be expected. There has been increasing cognizance of the importance of physical activity, emotional reactivity and consumption of tobacco in any preventive programme but the relationship of these factors to levels of cholesterol in the blood is uncertain.

In the search for an efficacious hypocholesterolemic agent a wide sample range has been offered, viz. sitosterols, estrogen hormones, thyroid analogues, nicotinic acid and more recently triparanol. The latter as a known inhibitor of the synthesis of cholesterol would appear to be potentially the most promising of these agents, but whether desmosterol and like compounds which are released after the administration of triparanol have any atherogenic properties has yet to be clarified. Meanwhile, in any programme for lowering blood cholesterol the impressive effect of nicotinic-acid therapy in some patients commands careful attention.

With nicotinic-acid therapy it has been maintained that significant, sustained and

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reproducible reductions in the concentration of cholesterol in serum can be achieved in the majority of hypercholesterolemic patients, and that besides being effective this therapy is practical and probably free from serious harmful effects.[1] Altschul, Hoffer and Stephen[2] were first to record that large doses of nicotinic acid—but not the amide—would depress the serum cholesterol in human subjects, whether normal or hypercholesterolemic. Initially they had noted the hypocholesterolemic effect when nicotinic acid was administered to rabbits. Altschul[3] also observed that when it was given for longer periods, nicotinic acid reduced the incidence of experimental atheromatous lesions in cholesterol-fed rabbits, a finding which was confirmed by Merrill and Lemley-Stone.[4] On the other hand, Hunter and Wong[5] report that when nicotinic acid is fed to cockerels on a high-cholesterol diet, it has no apparent effect on aortic atheromatosis nor is there any reduction in the level of cholesterol in the blood of these animals.

Earlier reports of the effectiveness of nicotinic acid in man by Parsons and associates,[6] Parsons and Flinn [7] and others were sufficiently encouraging to warrant long term clinical trials. Several progress reports have been published in recent years.[1,9,19] Achor and associates[1] found that the average decrease in the concentration of cholesterol in the blood was 16 per cent in 33 patients given 3 grams daily for 3 months; they noted that patients with higher initial cholesterol values usually obtained a greater response than did those with lower pretreatment values. Parsons and Flinn[9] noted a 19 per cent average reduction in the levels of cholesterol in 26 patients after the first 3 months of treatment, a group with a mean pretreatment cholesterol level of 325 mg. per 100 ml. More recently, Hunter[19] observed that a 23 per cent mean reduction in the levels of blood cholesterol was achieved after 3 months of therapy using a dosage regimen of 3 grams daily in a similar group of patients. All reports indicate a wide variability of response from patient to patient. Some have indicated the effectiveness in refractory patients of further increasing the daily dose of acid above 3 grams.[1,9] Achor and his colleagues have reported that responses have been maintained for periods up to 2 years.[1,11]

The efficacy of nicotinic-acid therapy is perhaps enhanced by some expectancy of symptomatic improvement in patients with severe anginal symptoms. This is stressed by Hunter [19] who draws particular attention to the dramatic improvement in severity and frequency of angina of effort in some patients. Although great caution must be exercised before drawing too many conclusions from these subjective manifestations, they cannot be dismissed lightly. Further controlled appraisal is to be awaited with interest.

Offsetting the therapeutic responsiveness to the drug is the troublesomeness of some side effects which necessitates the early discontinuation of treatment in about 20 per cent of the subjects.[19] Flushes, pruritus and prickling of the skin are common symptoms which usually settle or become quite tolerable within a week or two. On the other hand, gastrointestinal disturbances, with symptoms such as nausea, anorexia, dyspepsia, or abdominal colic, are more discomforting and are usually the main reason for abandoning therapy. High acidity may be a factor in promoting gastric upset, and some patients manage better on a buffered solution of the drug.[19,21] No definite more serious side effects have been recorded.

The mode of action of nicotinic acid in lowering the level of cholesterol in the blood remains obscure. Several hypotheses have been proposed: (1) that of Altschul [12] who suggested that the reduction in blood cholesterol is achieved as a result of enhanced oxidation of cholesterol to more readily excretable oxycholesterols, and (2) that of Merrill and Lemley-Stone [4] who, after finding that nicotinic acid was excreted partially as a methyl derivative, postulated that this may deplete the body of methyl and acetyl groups, and that this reduction influences the rate at which cholesterol is synthesized from acetate groups. It was also of some interest to note the suggestion of Friedman and Byers that the hypocholesterolemic property of nicotinic acid may be due to an anorectic effect. These investigators presented experimental evidence which conflicts with

that of previous workers, indicating that when there is strict control of the high dietary intake of fat-cholesterol in both the treated and the control animals, the ingestion of nicotinic acid did not prevent the expected hypercholesterolemia. They commented on the lack of strictly controlled dietary regimens in the reported series of clinical trials, as well as on the absence of published changes in weight in the patients. They went on to speculate that a potential nauseant (like nicotinic acid) operating at a subclinical level might induce a reversion to food of a lighter less lipid-containing nature. Certainly loss of weight has been a feature in some but not all patients on this drug.[13,14]

If a more tolerable preparation of nicotinic acid becomes available, this drug might prove to have a more readily acceptable place in the coronary therapeutic armamentarium. As long as the mode of action is obscure certain restraint in its use is to be expected. Currently nicotinic acid would seem generally to be as effective as any other hypocholesterolemic agent—perhaps more so. More thorough pharmacologic investigations of its action would seem to be a worth while gambit.

REFERENCES

1. Achor R. W. P., Berge, K. G., Barker N. W. and McKenzie, B. F. Treatment of hypercholesterolemia with nicotinic acid, Circulation 17:497 1958.
2. Altschul, R., Hoffer A., and Stephen, J. D. Influence of nicotinic acid on serum cholesterol in man, Arch. Biochem. 54:558, 1955
3. Altschul, R. Die Beeinflussung des Blutcholesterinspiegels und der experimentellen Atherosklerose durch Nikotinsäure, Ztschr Kreislaufforsch. 45:573 1956.
4. Merrill, J. M. and Lemley Stone J. Effects of nicotinic acid on serum and tissue cholesterol in rabbits, Circulation Res. 5:617 1957
5. Hunter J. D. and Wong L. C. K. Effect of nicotinic acid on cholesterol levels and atheroma lesions in cockerels, A.M.A. Arch. Path. (in press)
6. Parsons, W. B. J., Achor R. W. P. Berge, K. G. McKenzie, B. F. and Barker N. W. Changes in concentration of blood lipids following prolonged administration of large doses of nicotinic acid to persons with hypercholesterolemia. Preliminary observations, Proc. Staff Meet. Mayo Clin. 31:377 1956.
7. Parsons, W. B. J. and Flinn, J. H. Reduction in elevated blood cholesterol levels by large doses of nicotinic acid, J. A.M. A. 165:234 1957
8. O'Reilly P. O. Callbeck, M. J. and Hoffer A. Sustained-release nicotinic acid (Nicospan) Effects on (1) cholesterol levels and (2) leukocytes, Canad. M.A.J. 80:359 1959
9. Parsons, W. B., Jr., and Flinn, J. H. Reduction of serum cholesterol levels and beta-lipoprotein cholesterol levels by nicotinic acid, Arch. Int. Med. 103 783 1959
10. Hunter J. D. Nicotinic acid therapy in patients with coronary disease, New Zealand M. J. 59:280 1960
11. Achor R. W. and Berge K. G. Treatment of hypercholesteremia with large doses of nicotinic acid, Med. Clin. North America 42:871 1958
12. Altschul, R., and Hoffer A. Effects of salts of nicotinic acid on serum cholesterol, Lancet 2 713 1958.
13. Altschul, R. Niacin (nicotinic acid) and serum cholesterol, J.A.M.A. 166:822, 1958.
14. Friedman, M. and Byers, S. O.: Evaluation of nicotinic acid as an hypocholesteremic and antiatherogenic substance. J. Clin. Invest. 38:1328, 1959

Clinical communications

Studies with a new coronary vasodilator drug: Persantin

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In 1959 Kadatz reported the potent coronary vasodilator properties of a new chemical compound, Persantin (2,6-bis (diethanolamino)-4,8-dipiperidino-pyrimido-(5,4-d) pyrimidine).† When used in low dosage in experimental animals, Persantin has been shown to exert a most powerful coronary vasodilator action without substantially altering the work of the heart[1] or its oxygen consumption.[2-4] Reports on its value for the relief of angina pectoris in man have been conflicting; some investigators have reported remarkable beneficial effects,[5-] which others have not been able to confirm.[17,18]

Our study was designed to determine specifically whether this drug was of therapeutic value to patients suffering from long-standing angina pectoris. The studies reported below were performed in three phases.

It was first necessary to determine by catheterization of the coronary sinus that Persantin was as effective a coronary vasodilator in man as in experimental animals and to determine the duration of such effects after intravenous administration. Next, we studied the effect of an appropriate intravenous dose of Persantin on the pain and electrocardiographic changes induced by exercise in a series of patients with angina pectoris. Finally, we considered the possibility that Persantin given orally over a longer period of time might have therapeutic effects which were not discernible after a single intravenous injection. Thus a therapeutic trial of oral medication in anginal subjects was undertaken.

Influence of Persantin on coronary sinus oxygen saturation in man

Six patients with heart disease were selected for study (Table I). In 3 of these there was no reason to suspect coronary disease, and in 3 there was severe angina pectoris with typical pain and typical electrocardiographic change on effort. Under light sedation (Demerol, 25 mg., Nembutal, 100 mg.) the catheter was passed approximately one and one-half inches into the coronary sinus. The location of the catheter and the absence of obstruction were determined by fluoroscopy, pressure monitoring, and the withdrawal of samples of blood. In 3 subjects the tension time index per minute was determined from the brachial arterial pressure curve (Sanborn

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Table I Maximal change in coronary sinus oxygen saturation after Persantin

Subject	*Sex*	*Age (yr.)*	*Diagnosis*	*Coronary sinus oxygen saturation (%)*	
				Control	*After Persantin*
M B	M	16	Pulmonic stenosis	19 1	32 0
M L	M	42	Rheumatic heart disease Mitral stenosis	38 2	46 5
V C	M	19	Atrial septal defect	35 0	38 0
H O	M	53	Arteriosclerotic heart disease	39 7	47 3
M D	M	52	Arteriosclerotic heart disease	37 7	52 4
R C	M	35	Arteriosclerotic heart disease	48 2	54 4

Table II Changes in arterial mean blood pressure heart rate and tension time index per minute in 3 subjects after Persantin

Subject	*Sex*	*Event*	*Mean blood pressure (mm. Hg)*	*Heart rate*	*Tension time index/min (mm. Hg sec./min.)*
H O	M	Control	116	83	2 696
		After Persantin	128*	94	3 610
M D	M	Control	67 5	72	1 265
		After Persantin	63 0	78	1 280
R C	M	Control	107 5	74	1 034
		After Persantin	102 5	86	1 064

*During attack of angina.
Values concurrent with Table I

267B differential transducer) Sarnoff and co-workers[7] have shown that this value (an indirect index of the left ventricular force) relates closely to the oxygen consumption of the isolated heart. Without the patient being aware of any intervention 20 mg of Persantin diluted in 15 ml. of normal saline was injected over a period of 2 minutes through the catheter and samples of coronary sinus blood were withdrawn at 2 5 10 20 and 30 minutes thereafter

Results. Arterial oxygen values were normal in all subjects and did not change significantly after Persantin In all subjects except one a young man with interatrial septal defect and no evidence of coronary disease there was a significant increase in coronary sinus oxygen saturation (Table I) This change was maximal at 2 to 5 minutes after injection and diminished to zero by 20 to 30 minutes. It was evident in the 3 subjects with arteriosclerotic heart disease that this was not the result of a reduction in energy expenditure by the heart, as reflected by the tension time index nor could it have been the result of increased coronary perfusion pressure (Table II) We concluded that this substance was producing increased coronary flow even in the presence of severe coronary disease.

Comment The changes in coronary sinus oxygen saturation are similar to those reported by Knipping and associates[11] In the presence of constant arterial pressure and oxygen saturation an intervention which causes a rise in coronary sinus oxygen saturation may have acted in three ways by reducing the energy requirement and hence the oxygen demand of the heart muscle by altering myocardial metabolism in such a way as to reduce the oxygen consumption per unit energy released or b

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exactly the same length of time would repeatedly bring on anginal pain with electrocardiographic changes throughout the period of study. However, in spite of this the anginal threshold was never assumed to be constant, and trials of Persantin or nitroglycerin were always preceded by a control exercise test. In one subject only did the exercise tolerance change substantially during the period of observation and 2 months after the anginal threshold was established a positive test could no longer be obtained even at greatly increased exercise loads.

The results of each exercise test were assessed separately with respect to symptoms and electrocardiographic changes. As regards the former, a test was considered to be positive when typical anginal pain was provoked. Electrocardiographic criteria for a positive test were a flat or sagging depression of the RS-T segment of 1 mm. or more below the P-Q level in a left ventricular unipolar lead recorded each minute for 5 minutes after the end of exercise.[23] This was frequently associated with the appearance of a completely flat, diphasic, or inverted T wave.

Results. In all, there were 19 trials of intravenous Persantin in 12 subjects. In 3 subjects electrocardiographic changes of ischemia were observed after the injection but before the commencement of exercise. After exercise, ischemic changes still appeared in 18 out of 19 trials in spite of the administration of Persantin (Table III) and the apparent protective effect in this one trial could not be repeated on subsequent occasions. In 6 out of 19 trials Persantin gave apparent protection from anginal pain.

In 7 subjects the comparative effects of 0.6 mg. of nitroglycerin sublingually and 20 mg. of Persantin intravenously were studied on one occasion each (Table IV). Nitroglycerin gave "electrocardiographic protection" in 6 and symptomatic protection in all 7 subjects. By contrast, Persantin failed to give "electrocardiographic protection" in any and prevented the occurrence of anginal pain in only 3.

Comment. The electrocardiographic changes observed in 3 subjects after the administration of Persantin but before the onset of exercise may well have [illegible] result of pain and anxiety as a result of the intravenous injection. It is unlikely, however, that these factors were still present at the time of onset of exercise 5 minutes later, by which time the electrocardiographic changes had reverted to normal.

The preliminary catheterization studies reported above would suggest that the dosage employed should have produced some increase in coronary flow in these patients. The failure to protect them from pain and electrocardiographic changes on effort suggests that any vasodilatation which occurred must have taken place in areas of heart muscle other than the site of the ischemia. By contrast, the protection afforded by nitroglycerin in these subjects was notable. In the face of the evidence, one must conclude either that nitroglycerin produced an increase in flow in the ischemic area when the powerful dilator Persantin had failed, or that the beneficial effect of nitroglycerin is not the result of coronary vasodilatation at all. The latter conclusion would seem to be the more likely.

Therapeutic studies with oral medication

In view of the favorable reports in the literature it was considered possible that oral medication carried out for a longer period of time might have some therapeutic effect not apparent in the acute studies reported above. Accordingly, two studies were designed to test this possibility in a small, highly selected group of subjects who had reproducible angina of effort with electrocardiographic changes, freedom from other complaints, and who appeared to be reliable witnesses. In both studies the subjects continued with their previous medication and previous daily routine but kept records of the number of attacks of pain, the number of nitroglycerin tablets consumed, and their general subjective impression of their clinical status. Each subject was followed by the same physician throughout the course of the studies and on the basis of the patients' weekly reports they were assessed as being "improved," "unchanged," or "worse."

Double-blind study. The first study, which involved 13 trials in 11 patients, was conducted on a double-blind basis. The [illegible]

edge of which tablet was Persantin and which was the placebo was retained by the *suppliers until the end of the trial and each* trial was commenced with one or other tablet alternately Duration of therapy and dosage was varied as follows 5 trials of Persantin (37 5 mg daily in 3 doses) and placebo given alternate weeks for a total of 4 weeks 8 trials of Persantin (100 mg daily in 4 doses) and placebo given alternate months for 2 months.

On the lower dosage regimen one patient was improved on Persantin only One was improved on placebo only and 3 patients reported no change with either tablet On the higher dosage one patient reported improvement on placebo only (the same patient who had apparently benefited from placebo on the lower dosage)

Given in this manner Persantin was clearly of no therapeutic benefit to the patients. However there was a possibility that higher dosage might be necessary to secure adequate levels of the drug in the blood and this was accordingly tried

Therapy with high oral dosage Five cooperative patients were selected on the basis of the same criteria used for the double blind study These patients were given 225 mg of Persantin daily divided into 3 doses, 30 minutes before each meal. No attempt was made to use a placebo

Two subjects were unable to continue the trial for more than 1 week because of severe nausea and cramping abdominal pain which appeared to be related to the medication Of the 3 subjects who continued the treatment for 6 weeks, 2 were unchanged and 1 reported a *reduction in his* attacks. This improvement however was not reflected in his report cards which indicated the same number of attacks and the same consumption of nitroglycerin tablets. Finally the anginal threshold during treadmill exercise was unaltered at the end of the 6 weeks of therapy in these subjects.

Comment In spite of the reports of noticeable benefits from oral dosage as low as 35 mg daily there is now evidence that with such dosage the levels of Persantin in circulating blood in most subjects would be extremely low [22] and subsequent reports in the literature have failed to confirm the efficacy of Persantin in this dosage.[13,14] For this reason doses up to 225 mg per day were tried It would be inaccurate to report therapeutic failures at this dosage level because of the small number of patients involved but there was clearly no therapeutic effect from the intermediate dosage of 100 mg per day

Discussion

The number of patients involved in these studies was small and negative conclusions based on them do not preclude the possibility that a small percentage of patients might receive some benefit from Persantin However a small carefully conducted trial with a highly selected group of patients may give worth while information Thus, the value of nitroglycerin was amply demonstrated in the exercise study employing only 7 subjects. By contrast in the same study no clear benefit resulted from Persantin There can be no doubt that Persantin given orally or intravenously does not approach nitroglycerin in value for this purpose

These results suggest that the mechanism of action of nitroglycerin should be reviewed This drug like all others employed for relief of angina is generally considered to act through the mechanism of coronary vasodilatation True coronary vasodilatation in the presence of a constant perfusion pressure will result in an increase in coronary flow in excess of demand with a consequent increase in coronary sinus oxygen content Therapeutically effective dosage levels of nitroglycerin however could not be shown by Gorlin and his co-workers[23] to have any such effect in man an observation which we have confirmed in as yet unpublished studies. It is thus anomalous that Persantin a potent coronary dilator has failed to benefit patients with angina pectoris, whereas nitroglycerin which apparently is not a true dilator remains the most useful medication known for the relief of this condition It is pertinent to observe that there is no vasodilator drug which has an undisputed place in the relief of angina pectoris and nitroglycerin would appear to act in some other manner which we are currently endeavoring to determine

This conclusion does not imply that there is no therapeutic place for coronary

dilator drugs such as Persantin. There is evidence which suggests that coronary spasm might well complicate, if only temporarily, acute coronary occlusion[24] and the use of such drugs at the time of infarction or of sudden aggravation of angina might well be worth a trial.[25]

Conclusions

1. By coronary sinus catheterization evidence was obtained that 20 mg. of Persantin given intravenously might be expected to produce a significant increase in coronary flow for 10 to 20 minutes, even in subjects with ischemic heart disease.

2. A similar dosage given to patients with angina pectoris failed to prevent the occurrence of ischemic changes in the electrocardiogram on effort, although in 6 of 19 trials it appeared to prevent the onset of pain.

3. By contrast, 0.6 mg. of nitroglycerin sublingually prevented pain in 7 out of 7 exercise tests and prevented ischemic changes in the electrocardiogram in 6 out of 7 tests.

4. Persantin given orally in dosages up to 100 mg. per day appeared to have no therapeutic effect in patients with angina pectoris. Dosage of 225 mg. per day produced gastrointestinal symptoms in 2 subjects, and gave no benefit over a period of 6 weeks in 3 others.

5. The findings provide indirect evidence that the beneficial effects of nitroglycerin in patients with angina pectoris are not the result of coronary vasodilatation.

REFERENCES

1. Kadatz, R.: The pharmacology of 2,6-bis (diethanolamino)-4,8-dipiperidino-pyrimido-(5,4-d)-pyrimidine, new compound with coronary dilatory properties, Arzneim.-Forsch. 9:39, 1959.
2. Doerner, J., and Wick, E.: Comparative investigation of the efficacy of generally used coronary vasodilators in anesthetized and unanesthetized dogs, Arzneim.-Forsch. 10:631, 1960.
3. Bretschneider, H., Frank, A., Bernard, U., Kochsiek, K., and Scheler, F.: The effect of a pyrimido-pyrimidine derivative on the oxygen supply to the myocardium, Arzneim.-Forsch. 9:49, 1959.
4. Kiese, M., Lange, G., and Resag, K.: The effect of 2,6-bis (diethanolamino)-4,8-dipiperidino-pyrimido-(5,4-d)-pyrimidine on the blood flow in the experimentally induced myocardial infarct and in the healthy myocardium, Ztschr. ges. exper. Med. 132:426, 1960.
5. Fischer, E. K., and Fiegel, C.: Increase in oxygen supply to the myocardium by one of a new derivative of the pyrimido-pyrimidine group, Deutsches med. J. 10:484, 1959.
6. Hamm, J., Renschler, H. E., and Zack, W. J.: Clinical studies on the action of Persantin in angina pectoris, Medizinische 3:120, 1959.
7. Leingardt, H.: A contribution to the treatment of coronary insufficiency, Medizinische 49:2405, 1959.
8. Dutsch, L.: The treatment of coronary insufficiency, Therap. Gegenw. 99:228, 1960.
9. De Castro, B., and Parchi, C.: Preliminary results of tests with a new coronary dilator derived from pyrimido-pyrimidine (RA 8), Gior. clin. med. 41:1, 1960.
10. Jenneman, P.: Persantin, a new compound for the treatment of coronary insufficiency, München. med. Wchnschr. 101:340, 1959.
11. Pabst, H. W.: The action of a new coronary dilator, 2,6-bis (diethanolamino)-4,8-dipiperidino pyrimido (5,4-d) pyrimidine, Med. Klin. 84:257, 1959.
12. Foulds, T., and Mackinnon, J.: Controlled double-blind trial of "Persantin" in treatment of angina pectoris, Brit. M. J. 5202:835, 1960.
13. Zion, M. M., and Bradlow, B. A.: A controlled clinical trial of "Persantin" (RA 8) in angina pectoris, South African M. J. 35:11, 1961.
14. Deuchar, D. C.: Oral Persantin, Brit. M. J. 5230:967, 1961.
15. Reynell, P. C.: Intravenous Persantin, Brit. M. J. 5235:1318, 1961.
16. Dewar, H. A., and Stanley, H.: Oral Persantin, Brit. M. J. 5232:1107, 1961.
17. Sarnoff, S. J., Braunwald, E., Welch, G. H., Case, R. B., Stainsby, W. N., and Macruz, R.: Hemodynamic determinants of oxygen consumption of the heart, with special reference to the tension time index, Am. J. Physiol. 192:1, 1958.
18. Knipping, H. W., Bolt, W., and Mikulka: Clinical and experimental research with a new pyrimido pyrimidine derivative, Arzneim.-Forsch. 10:364, 1960.
19. Spitzbarth, H.: Cardiovascular function studies and clinical observations with 2,6-bis (diethylamino) 4,8-dipiperidino pyrimido (5,4-d) pyrimidine, Arzneim.-Forsch. 9:53, 1959.
20. Hoeckerts, Th., and Boegelmann, G.: Studies of the action of 2,6-bis(diethylamino)-4,8-dipiperidino-pyrimido-(5,4-d) pyrimidine, Arzneim.-Forsch. 9:47, 1959.
21. Wood, P., McGregor, M., Magidson, O., and Whittaker, W.: The effort test in angina pectoris, Brit. Heart J. 12:4, 1950.
22. Beisenherz, G.: Unpublished data.
23. Gorlin, R., Brachfeld, N., MacLeod, G., and Bopp, P.: Effect of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work, Circulation 19, 1959.
24. Gensman, S. N., Swenson, E., and Jones, M.: Intercoronary reflex demonstration by coronary angiography, Fed. Proc. 20:10, 1961.
25. Peel, A. H.: Persantin, Brit. M. J., 1961.

The implications of patterns of occlusion in arteriosclerosis

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With the advent of operative approaches to the arteries came the necessity for an exact localization of the lesions of arteriosclerosis. So far, more of such data are available for the lower extremities than for other parts of the body. As more information is gained, it becomes apparent that certain patterns of the arterial involvement may be expected in certain clinical situations. As examples, I may cite the youth of patients with occlusion commencing in the aortic bifurcation, the tendency for diffuse arterial involvement in diabetes, and the association of pulmonary arteriosclerosis with previous pulmonary embolism (or hypertension. These associations strongly suggest that arteriosclerosis is not a disease per se, but rather the end result of a variety of causative disease states.

There are additional indications that some sites of initial involvement are associated with relative discreteness of disease, others with diffuseness. This, in turn, carries an implication of varying prognosis, since diffuse disease involves many areas in the body and also shows a tendency to a more rapid progression of disease.

I will attempt in this paper to review what is known of the locations of arteriosclerosis, with some consideration of the means of recognizing the lesions in these places, and I will mention the varying prognoses which attach to different sites of involvement.

Anatomic factors in the effects of occlusion. Peculiarities in the anatomic pattern of the arteries, particularly with respect to their anastomotic connections, are important in varying the effects of occlusion from one site to another and between individuals as well.

Ischemia of a limb often fails to follow a glove or stocking distribution because of a relative circumscription that exists for the blood supply to muscle, nerve, and even to portions of the integument.[1a] For this reason, ischemia may be limited to parts of an extremity, as may be seen in interruption to the vessels of a viscus in the abdominal cavity. Thus, because of occlusion of the hypogastric artery, claudication often persists in the buttock after successful restoration of flow to the rest of the limb. Similarly, a neuritis or a cutaneous infarct may be due to an occlusion of the nutrient artery to those parts quite out of proportion to the vascular status of the limb as a whole.

Unexpectedly severe ischemia may occur in organs with multiple sources of supply if the anastomoses between these sources are imperfect. A detailed consideration

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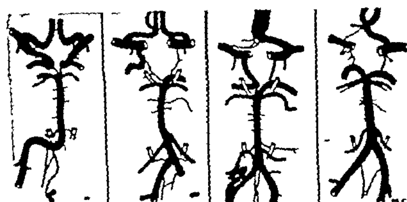


Fig. 1. Examples of discontinuity of the cerebral arterial circle and of preponderance of an internal carotid or vertebral artery (after Hasebe). (From Edwards, Surg. Gynec. & Obst. August 1955 by permission.)

of variations in collaterals may be found in a former article.[9] Aberrant interruptions in expected anastomoses are exceedingly common. For example the cerebral arterial circle shows a break or filiform segment in about 24 per cent of the cases. The expected arcade between the ileocecal and the right colic branches of the superior mesenteric artery is lacking in 5 per cent.[19] The arcades which connect adjacent arteries of the jejunum are minute or broken at some point in about 20 per cent of the cases. The palmar arches are often undeveloped with loss of adequate pulsatile flow to the hand on obstruction of either the radial or ulnar arteries.

The vulnerability of a part is further increased if there is great inequality in size and extent of the partners in an anastomosis. Schlesinger[23] noted the great mortality incident to obstruction of a preponderant coronary artery. Similar inequality in size of the two carotid or two vertebral arteries may give rise to unusually extensive changes when the larger one of a pair is occluded (Fig. 1). In the spinal cord occlusion of the arteria radicularis magna or some other of the major members of the supplying arteries, is most often responsible for the myelitis of arteriosclerosis.

Ischemic effects are especially prone to develop in areas in which vessels meet to join as collaterals. Such a region, which I have designated as a junctional zone,[9] lies, as it were, at the acral point of distribution of each of the partner arteries. Examples are the tip of a finger or toe or the interventricular septum of the heart.

Recognition of occlusion sites. Although arteriography remains the most certain way to establish the site of the arterial occlusion certain details of history or examination are helpful and find application in various parts of the arterial system.

The subjective complaints of the patient are, of course, the first clues to the diagnosis. Some of the syndromes caused by occlusion of the visceral arteries are being elucidated only currently. In the limbs the location of symptoms is often the location of the significant occlusion. Thus ischemic pain in the foot means occlusion of the small distal arteries whether or not additional proximal occlusion exists. The pain of claudication is only slightly less well localized. With the notable exception of claudication in the calf, pain over a muscle group points to obstruction of the particular artery which supplies that group.

Simple physical examination of the arteries is usually highly rewarding. Palpation of the arteries should be supplemented by auscultation. In 1952 Edwards and Levine[1] established that a systolic murmur can be heard over approximately 50 per cent of the larger arteriosclerotic arteries. This murmur is loudest close to the point of obstruction; it may be accompanied by a palpable thrill and its presence is generally indicative of a high grade of obstruction (Fig. 2).

Observation of the pulse or the arterial pressure is easily accomplished at \

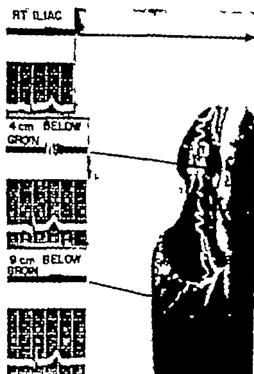


Fig. Phonoarteriogram demonstrating a systolic murmur loudest near the site of incomplete obstruction. (From Edwards and Levine: A.M.A. Arch. Int. Med. September 1952, by permission.)

levels of the limb through the use of an oscillometer such as the Pachon instrument. Elsewhere direct cannulation of the artery is required. We have found registration of the pulse volume in the extremities *to be very helpful in establishing the degree* and location of arterial obstruction as well as its localized or diffuse nature[12, 4] (Fig. 3).

Functional tests are particularly helpful in localizing obstruction in the visceral arteries or their branches, as exemplified by electroencephalography, electrocardiography, or split function tests of the kidneys. Certain maneuvers allow further deductions from these tests, for example, noting the effect of lowering blood pressure or the compression of a carotid artery upon the electroencephalogram, or the effect of exercise upon the electrocardiogram.

Occlusions in the pathways of the lower extremity

Aorta and iliac arteries. Limited occlusions are less frequent in the aorta or the iliac arteries than in the femoral or popliteal arteries. When the occlusion is limited to the aortic bifurcation, the clinical picture is strikingly different from that observed when it commences diffusely in the aorta or in the iliac arteries. Patients with the aortic bifurcation process are apt to be young, the process is sharply limited with many years of freedom from involvement of arteries either in other parts of the limbs or in the viscera. Pathologically, there is minimal involvement of the arterial wall and a thrombus forms the major part of the obstructing mass (Fig. 4).

An occlusion which starts in the iliac artery is almost invariably bilateral and is associated with diffuse disease of the aorta, the distal arteries, and the arteries of the viscera.

In an analysis of aortograms made in cases of aorto-iliac disease, Edwards and Lemay[17] found an accompanying obstruction of the testicular or ovarian arteries

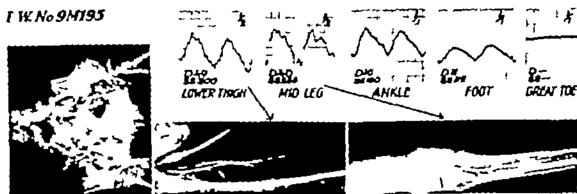


Fig. 3. Pulse registration by external cuff in patient with occlusion of the iliac, femoral, and tibial arteries. The fractions indicate recording attenuation, D, mean pulse amplitude, S, steepness of systolic slope. These values are abnormally low, with progressive diminution down the limb. The absence of a dicrotic notch and the aberrant vibrations are likewise characteristic of obstruction.



Fig 4 Aortogram of the sharply localized obstruction of the aortic bifurcation in a 43-year-old man. He has suffered no additional occlusions in 7 years since endarterectomy (From Edwards New England J Med 256:875 1957 by permission)

on one or both sides in 76 per cent of the subjects, of the inferior mesenteric artery in 37 per cent and of one or both hypogastric arteries in 29 per cent The occlusion of the ovarian artery was presumably due to the intimal proliferation which occurs during the menopause Disease of the hypogastric artery may well be responsible for the severe neuritis of the lower limb which is seen in diabetes particularly since the large trunks of the lumbosacral plexus are normally nourished from branches of the hypogastric artery

When obstruction starts at the aortic bifurcation the distal arteries are apt to be quite normal as attested to by a lack of serious difficulty in the feet. A good reactive hyperemia may also be induced in response to a period of cuff occlusion at the ankle (Fig 5)

Partial obstruction of either the aorta or the iliac arteries may produce the phenomenon of claudication accompanied by palpable pedal pulses. This is indicative of the patency of the distal tree The observation that in these instances the peripheral pulse may disappear after exercise has been shown to depend on an exaggeration of the normal exercise effect of pulse increase in the muscular territories of the calf and the thigh at the expense of pulsation at pedal and digital levels.

Death in cases of aorto-iliac obstruction is often due to recurrent ascending thrombosis which occludes the mouth of a renal artery

Occlusions below the inguinal ligament Obstructions are often well localized in the superficial femoral and upper popliteal arteries and carry an excellent prognosis Occlusion of the profunda femoris is fairly rare and as mentioned has an increased incidence in patients with diabetes.[5] It carries an ominous prognosis for the limb since it destroys a most significant collateral pathway Occasionally the profunda femoris may be occluded before the other arteries of the limb Such occlusion gives rise to claudication in the muscles which the profunda femoris supplies that is the adductor and quadriceps femoris groups

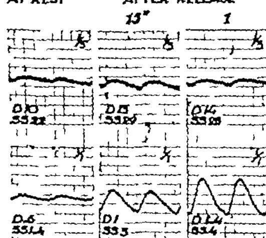


Fig 5 Pulse registration of the reactive hyperemia in the foot (*top*) and great toe (*bottom*) after release of constricting cuff at the ankle in a patient with occlusion of the aortic bifurcation similar to that shown in Fig 4 The dilatability of the distal vessels is indicative of their freedom from disease. (From Edwards and associates Am J Cardiol 4:572, 1959 by permission.)



Fig. 6. *Left.* Postamputation arteriogram of an arteriosclerotic limb from a patient without diabetes. *Right.* Arteriogram of a limb amputated from a young girl who had sarcoma of the femur. The normal arterial tree is fed by the anterior and posterior tibial and peroneal arteries. The heel is supplied by a large lateral calcaneal artery from the peroneal artery and several smaller medial calcaneal arteries from the origin of the lateral plantar artery. In the arteriosclerotic limb there is total occlusion of the posterior tibial artery and its two plantar divisions, along with closure of the calcaneal arteries.

Occlusion of the lower popliteal artery is characteristically associated with additional disease in the tibial and even the pedal vessels. Again patients with diabetes are more prone to this pattern than are others. Recently in our laboratory a study of limbs which were subjected to arteriography after amputation showed that occlusions in these instances involve many of the small arteries in the foot, heel, and toes[9] (Fig. 6). The plantar metatarsal and common digital arteries are almost universally occluded in the diabetic patient, and here and there short segments of proper digital arteries are also occluded. Similar occlusions of the small arteries were demonstrated in the limbs amputated from nondiabetic patients with arteriosclerosis, although such occlusions were possibly less diffuse than in diabetic patients.

The manifestations of such widespread disease are those of the severest grades of ischemia. The oscillometer usually gives a reading close to zero at calf level as well as at ankle level. As it is followed distally the recorded pulse shows progressive deterioration, and reactive hyperemia often cannot be demonstrated.[16] Such a picture gives the gloomiest prognosis, and efforts to restore the circulation fail. In a 5-year and then a 10-year follow-up study of 100 patients subjected to sympathectomy, the behavior in such cases revealed certain implications of this diffuse disease.[11] The results in such limbs were poor, and

likewise there was evidence of rather symmetrical involvement and a high incidence of disease scattered throughout the body including the coronary and cerebral areas. It was evident that the disease when diffuse was more rapidly progressive in both the preoperative and postoperative courses. In this way patients who had a poor local postoperative result had a poorer life expectancy than did those who had a more localized disease and a good postoperative result.

The distal disease just considered is part of a diffuse process present at high levels especially in the tibial system There are instances of more localized foci of obstruction in the pedal arteries accompanying localized occlusions at higher levels In the upper extremity this form is often manifested by the appearance of Raynaud's phenomenon late in life A murmur over the subclavian artery may complete the picture In a third form which involves both feet and less often the hands, multiple but discrete occlusions may be present in the acral parts of the limb with coldness and moderate discomfort but with little tendency to proximal progression or to the production of gangrene (Fig 7)

The arteries at large

The literature on vascular disease of the viscera is extensive but conclusions must be regarded as tentative because studies have generally been directed either to the larger or the smaller vessels and only occasionally to vessels of varying caliber in the same part It is especially difficult to know whether or not arteriolar disease so often described in visceral areas, is part of a disease which involves atherosclerosis of the larger arteries.

Aorta The special variety of localized obstruction of the bifurcation has been noted above.

Relatively diffuse disease in any outlying part is generally accompanied by extensive aortic involvement. In rare instances long stretches of the abdominal aorta may be totally occluded.

More commonly the lesions are occlusive only at the mouths of the branches of the aorta. Patients with symptomatic disease in the arteries of the lower limb often exhibit a loss of a subclavian or carotid pulse a difference in blood pressure between the two arms or murmurs over the origin of these arteries sufficiently frequent to dispel any idea that atherosclerosis

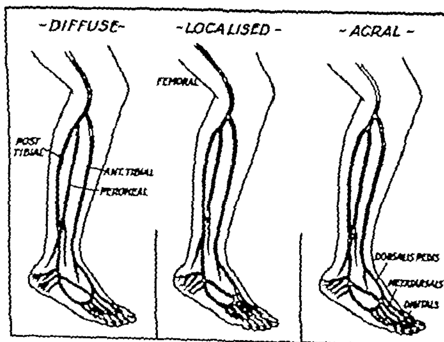


Fig 7 Three patterns of occlusion in the distal arteries of the lower limb.

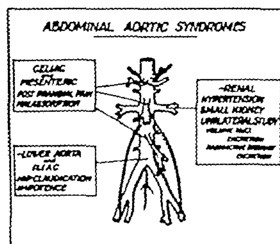


Fig. 3. Salient features in obstruction of the abdominal aorta or its branches.

shows any exceptional tendency to localize in the aortic arch. The disorder which is called pulseless disease or Takayasu's disease, with occlusion of these arteries in young women, by virtue of the clinical setting and the pathologic presence of arteritis deserves to be known as an entity called young female arteritis by Ross and McKusick.[22]

Coronary arteries. The predilection of *arteriosclerosis for parts of the coronary* arteries was documented in 1,200 hearts on postmortem examination by White and co-workers[25] and Ackerman and associates. In the order of diminishing severity of involvement the arteries were: left anterior descending, right main coronary, left circumflex, left main coronary, and the posterior descending. The *proximal* parts of all these arteries were the more severely involved. Diabetes was associated *with more extensive disease.*

The postmortem studies of Blumgart and co-workers[4] indicated that here there was but little tendency to the sharp limitation encountered fairly frequently in the lower limbs. Swedlund *and associates*[19] *have* recently examined 112 hearts at autopsy with respect to the degree and extent of obstruction. Theoretically, localization compatible with operative restoration of the lumen was seen in 18 per cent of the hearts, a palliative operation might have been performed in 52 per cent, but the disease was too *diffuse for operation in* 30 per cent. The most severe *and diffuse* disease was seen in the hearts of the younger male subjects.

In the heart, as in the lower limb, the more severe ischemic symptoms are associated with diffuse disease. Thal and co-workers[18] state: "The patient with angina on effort appears to have diffuse disease of the whole coronary arterial system, while in the patients we have studied with angina on rest there appears to be an additional impairment of the collateral circulation. In the 50 patients we have now studied, there have been 2 instances of segmental arterial block."

Cerebral arteries. In 250 patients with cerebral arterial insufficiency studied by arteriography, De Bakey and associates found the significant lesions to be extracranial in 42 per cent. Usually, more than one of the three sources from the aorta are obstructed. This is considered to be the most favorable localization since a patent segment is invariably found above the obstruction, making a surgical reconstruction possible. Javid[11] indicates that the common carotid of either side may be involved as frequently as the origin of the internal carotids, whereas the external carotid is often quite normal.

The internal carotid artery is occluded at its origin about twice as frequently as at its terminal bifurcation into the anterior and middle cerebral arteries.[17,1,22] The intermediate part (the upper cervical and petrous segment) is not usually involved until complete closure below or above produces a propagated thrombus in this long *unbranched segment.*

Hutchinson and Yates[22] have demonstrated in postmortem dissection that a *rather diffuse arteriosclerosis of the vertebral* artery, especially of its cervical segment, is apt to accompany disease of the internal carotid artery.

With regard to the intracranial parts of *the cerebral circulation, Baker and Iannone*[2] found that the severest lesions of the large arteries of the circle of Willis were located in the bifurcation of the internal carotid artery into the anterior and middle cerebral arteries and the bifurcation of the basilar artery into the posterior cerebral arteries. The smaller branches *showed less involvement. The frequency of association of occlusion of the major*

source arteries and diffuse disease of the cerebral branches is uncertain. According to Baker and Iannone the fibrotic lesions of the small cerebral arteries and arterioles do not appear to accompany atherosclerosis of the larger arteries.

Major strokes or transient episodes of confusion or palsy constitute the most significant parts of the history in cerebral arteriosclerosis. The favored explanation for transient symptoms at present is the lowering of cerebral blood flow which is occasioned by falls in arterial pressure in the presence of narrowed cerebral arteries.[57] Other theories of causation are discussed by Hicks.[33]

Palpation of carotid pulses remains an important step in examination although it is impossible to ascertain whether a pulsation above the bifurcation comes from the internal or external carotid artery. Finally one may fail to detect a high pulsation when arteriography shows the artery to be patent. Tyler[61] puts considerable emphasis on the combination of exaggeration of the common carotid pulse (such as is known to occur proximal to an obstruction[13]) and absence of a pulsation high in the neck. Palpation is of course, not applicable to the vertebral artery.

The murmur of stenotic flow usually systolic, is often heard over the narrowed area in the subclavian artery (possibly at the vertebral origin) or the carotid arteries. A murmur that is heard over the skull or eyeball may denote an occlusion or a collateral vessel.

We have tried registration of the carotid pulse with a special pneumatic capsule but one cannot be sure whether the pulse above the bifurcation comes from the internal or external carotid artery and quantitation is invalidated by differences due simply to vagaries in application of the capsule. Ophthalmodynamometry is valuable in showing the fall in pressure in the ophthalmic artery due to arterial narrowing. Arteriosclerosis of the retinal arteries per se is a poor indication of arteriosclerosis in other parts of the cerebral circuits.[1]

The best localization here as in other parts of the body may be achieved by arteriography but ancillary data are to be sought in the electroencephalogram especially after separate compression of each common carotid artery.[37, 41] This may indicate the relative importance of flow through each carotid artery. The maneuver should be done carefully because of the theoretical danger of inducing cerebral ischemia. Electroencephalographic studies should precede angiography and may make the latter study superfluous.

Arteriosclerosis of the spinal cord has received less detailed study. In an excellent study Magfiulo[44] found the relatively small arteries of the cord proper involved in hyperplastic changes. This was more prominent when generalized arteriosclerosis was present but he made no specific examination of the arteries leading to the spinal cord.

Celiac and mesenteric arteries. Arteriosclerosis may obstruct one or rarely all three of the major arteries to the gastrointestinal tract. It was noted above that the inferior mesenteric artery was seen to be occluded in one third of our cases of aorto-iliac disease.

Data on localization of the obstruction in these visceral arteries are incomplete. Derrick and others[7] found that the narrowest area of obstruction in the three main arteries is most often within the proximal 1.5 cm. of their length with the remainder usually free of disease. There are no data, however on the state of the farther branches of the main trunks.

The outstanding symptom of intestinal arteriosclerosis appears to be postprandial abdominal pain usually periumbilical or right-sided. Significantly more pain is caused by a heavy meal than a light one.[34] Shaw and Maynard[57] have recently indicated that malabsorption of various substances including fats sugars and vitamin B_{12} can be demonstrated. Aortography with lateral views confirms the diagnosis.

Renal arteries. Blackman[4] found partial arteriosclerotic occlusion in one or both major renal arteries of subjects with hypertension along with atherosclerosis of the aorta and its branches. He found, as has Richardson,[53] that the process in the stem artery was most often localized in a short segment near the aorta. The larger intrarenal branches, including the interlobar arcuate and interlobular arteries, were however the seat of farther arteriosclerosis.

Bilateral bundle-branch block
Critical rates in ventricular conduction

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A condition of unstable conduction in the cardiac bundle branch system at a critical heart rate is well known. Incidence mechanism pathology duration and some clinical aspects have been discussed previously.[1-6] The purpose of this paper is to describe the occurrence of unstable conduction at a critical rate in bilateral bundle branch or intraventricular block with shifts from double to single block and vice versa— bloc à bascule[7] and to report observations in two cases one with autopsy findings.

Case reports

Case 1 M. P. a 78-year-old white man was admitted to Beth Israel Hospital on Feb. 6 1956, because of intermittent chest pain and shortness of breath which had been present for 1 month. On examination he appeared to be acutely ill, dyspneic and cyanotic. The heart was markedly enlarged. The heart sounds were faint and irregular. A Grade 2 to 3 (maximum of 6) holosystolic murmur was audible over the area of the aortic valve. The aortic second sound was louder than the pulmonic second sound but not abnormal. The blood pressure was 160/100 mm. Hg. Respirations were 28 per minute. Râles were heard in the right posterolateral lung field. The liver was moderately enlarged and tender. There was bilateral, Grade 4 pitting pretibial edema.

Laboratory data. The venous pressure at the antecubital space was 260 mm. of saline. It rose to 490 mm. on pressure over the right upper quadrant of the abdomen. The circulation time (arm to tongue with Decholin) was 23 seconds. The hemogram and erythrocyte sedimentation rate were normal. The blood nonprotein nitrogen was 38 mg. serum albumin 4.72 Gm. globulin 1.54 Gm. cholesterol 250 mg. esters 176 mg. and total serum bilirubin 1.75 mg. per 100 ml. Alkaline phosphatase was 17.8 Bodansky units, thymol turbidity was 2.2 units and cephalin flocculation was 2 plus in 48 hours. Serum electrolytes were sodium 113.8, potassium 3.8, and chlorides 93.5 mEq. per liter. Calcium was 8.8 mg. and phosphorus 3.8 mg. per 100 ml. Prothrombin time was 15.2 seconds, with a control of 14.1 seconds. A serologic test for syphilis was negative. An x-ray film of the chest revealed marked enlargement of the cardiac silhouette to the right and left. There was considerable increase in the bronchopulmonary vascular markings, which suggested severe pulmonary congestion. X-ray examination of the skull showed definite evidence of Paget's disease. The diagnosis was hypertensive and arteriosclerotic heart disease, old myocardial infarction, congestive heart failure Class IVE, and Paget's disease. The patient was treated with complete bed rest, a low-sodium diet, digoxin, Mercuhydrin, and sedatives. At the time of the first electrocardiogram, on Feb. 7, 1956, he received 1 mg. of digoxin orally that day, 0.5 mg. twice a day for the next 2 days, then 0.25 mg. daily. He responded well to treatment, and after 6 weeks was discharged, greatly improved.

Electrocardiograms. The first electrocardiogram (Feb. 7, 1956) (Fig. 1) showed a regular sinus rhythm, P waves of normal configuration, P-R interval of 0.22 second, and QRS of 0.16 second in duration, with large R waves in Lead I and deep S waves in Lead III. R was 30 mm. in Lead aVL, which suggested the presence of left ventricular hypertrophy. An S wave was not present in Lead I but the R-T junction was depressed 2.5 mm. and in Lead III the S-T was elevated 3.0 mm. In Lead V the intrinsicoid deflection time to R peak was 0.12 second and in Lead aV$_L$ and V$_6$ to R peak 0.09

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and 0.10 second, respectively. This evidence of delayed arrival of the activation potential over the free wall of both left and right ventricles laterally with normal activation time in between 0.055 second in Lead V₄ was indicative of bilateral bundle-branch (intraventricular) block (see later). The cardiac rate was 87 to 89.5 per minute.

In the second electrocardiogram (Feb. 10, 1956) (Fig. 2) the P-R interval was 0.22 to 0.24 second. QRS was slightly less wide, 0.13 to 0.14 second. The appearance of the standard limb leads was similar to that in the previous tracing except for the presence now of prominent slurring in the descending limb of R_1, and greater displacements of RS-T in Leads I and III, elevation of 8.0 mm. in Lead III as compared to 5.0 mm. previously. In Lead V₁ the intrinsicoid deflection time was still long, 0.11 second, but in Leads V₄ through V₆ it was reduced to 0.04 to 0.05 second and a deep S wave appeared in Leads V₄ through V₆, 20 mm. in Lead V₆. The T waves showed considerable change in shape in Lead V₁, and in Leads V₅ and V₆ they became upright although they had been deeply inverted in these two leads in the previous tracing. In Leads V₅ and V₆ T was no longer opposite in direction to the major QRS deflection. The normal intrinsicoid deflection time now in Leads V₅, V₆, and aV_L with the reduction of the QRS interval was good evidence that the left bundle-branch block had disappeared electrocardiographically. The persistently late intrinsicoid deflection in Lead V₁ indicated that right bundle-branch block was still present. The cardiac rate in the second tracing was 77 to 79. It appeared that the slowing from 87 to 89 contributed to the change in block with the critical rate between 79 and 87.

The third, fourth, and fifth electrocardiograms were taken on Feb. 15, 23 and 28, 1956. P-R intervals were slightly longer but constant at 0.24 to 0.26 second; the QRS duration was 0.15 to 0.16 second. The intrinsicoid deflection time in Lead V₁ was 0.11 second and in Lead V₆ it was 0.05 second. The heart rates were 65 to 70 per minute. On Oct. 20, 1956, when the electrocardiogram showed only single right bundle-branch block, the right and left precordial leads were recorded simultaneously on a multichannel electrocardiograph. Attempts were made to increase the cardiac rate by Master two-step exercise test, amyl nitrite, and atropine gr. 1/75 subcutaneously. The heart rate did not rise above 80 per minute and no change to bilateral bundle-branch block was registered. The peak of R in Lead V₁ was synchronous with the nadir of S in Lead V₆.

The second and final hospitalization was on June 3, 1957. During the previous 14 months he had received digitalis leaf 0.1 Gm. daily and occasional injections of Mercuhydrin. He appeared to do quite well until 5 days before this hospitalization when he developed increasing shortness of breath.

Physical examination revealed a heart rate of 30 and irregular occasional audible atrial sounds, blood pressure of 200/100 mm. Hg, distended neck veins at 90 degrees, bilateral basal râles, enlarged liver, and slight ankle edema. The laboratory findings were not significantly different from those of the previous hospitalization. However, the electrocardiogram now showed complete A-V block (Fig. 3) with changes in the configuration of QRS due either to (1) changes in the degree of block in the two bundle branches if the complete A-V block were produced by alterations in the A-V node or bundle of His with the ventricular pacemaker arising lower in the main bundle, or to (2) a change to an idioventricular pacemaker if each of the bilateral bundle-branch blocks had become complete. On June 8, 1957, 4 days before death, there was a return of A-V conduction with the P-R 0.4 second and the atrial and ventricular complexes similar to those of Feb. 15, 1956 (Fig. 2) except for a slightly smaller degree of right bundle-branch block.

He failed to respond to the usual cardiac therapy and died, 9 days after admission to the hospital. At necropsy the heart was enlarged and weighed 700 grams. The left ventricle was dilated and hypertrophied 1.9 cm. in thickness. There was generalized arteriosclerosis; the aorta and pulmonary arteries were affected. The right coronary artery was larger than the left, and its ostium was surrounded by atheromatous plaques. A conus artery* was present. Atheromatous and calcific foci with narrowing of the lumina, some eccentric, were present in both right and left coronary arteries and their main branches. On microscopic examination the myocardium of the ventricles, including the interventricular septum, showed many areas of hypertrophic muscle fibers, areas of fibrosis, and foci of hyalinization.

Case 2. I. T., a 72-year-old white man, was admitted to the Beth Israel Hospital on May 19, 1957, with a 2-day history of recurrent epigastric pain, which occasionally radiated to the left precordial area, and difficulty in breathing. There had been two previous admissions to this hospital, mainly for neurological complaints; the diagnosis was cerebral arteriosclerosis and probable chromophobe adenoma of the pituitary gland, with panhypopituitarism and extrasellar extension with involvement of the hypothalamus.

Cardiac complaints started in 1951, 6 years prior to the third and final hospitalization, when he suffered a myocardial infarction. This was followed by angina pectoris, dyspnea on slight effort, and intermittent ankle edema. For several years he received digitoxin and Diamox.

On examination on May 19, 1957, he appeared to be chronically ill and was suffering from mild pain in the epigastrium. The heart sounds at the apex seemed to be normal. Triple rhythm was not heard. A Grade 3 harsh holosystolic murmur was present at the apex, well transmitted over the precordium and to the neck. The pulmonic second sound was accentuated. The blood pressure was 124/76 mm. Hg. Moderately loud coarse râles were heard throughout both lung fields, more at the bases on inspiration and expiration, and not cleared by coughing. The liver was slightly enlarged. There was no edema and no tenderness of the calves.

Laboratory data. The routine urinalysis and blood count were normal. Hematocrit was 46 per cent and the erythrocyte sedimentation rate was 77 mm. per hour. The blood carbon dioxide was 30.2 volumes per cent, serum sodium was 134.6, potassium 5.4, and chlorides 91.7 mEq. per liter. The non-

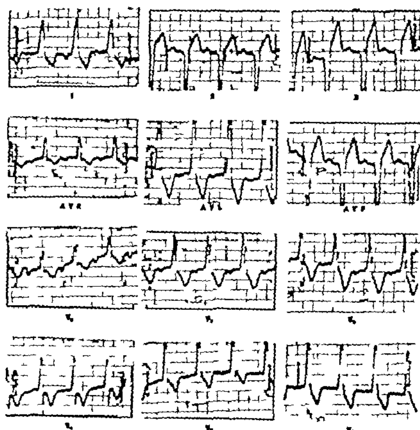


Fig 1 Case 1 Feb 7 1956 B lateral bundle-branch block Intrinsicoid deflection is late n Leads V nd V but not in Lead V Heart rate of 87 to 89

thrombin time w 13 8 second nd tr nsaminase (C.O.T) w 22 un t Venous pressure n the antecubital spa e w 105 mm of saline and the arm-to-tongue irculation time with Decholin as 30 seconds A hest film revealed the heart to be generall enlarged w th ongested lung fields nd obliteration of the left ostophrenic sinus The diagnoses w arterio-clerotic heart disease old myocardial infar tion coronary nsufficiency cardiac failure especially of the left side, and chronic bronchitis

Electrocard ogram On July 17 1953 the electrocardiogram showed a pattern of right bundle-branch block and infar tion of the anterior and diaph gmatic alls of the left entricle The heart rate w 60 to 70 per minute P R w 0 15 second and QRS w 0 12 second The R in Lead V and V a 7 mm with the peak 0 065 second f om the onset f QRS Tracings on April 22 (F g 4) nd April 23 195 were t ardiac tes of 90 and 95 P R w 0 16 and 0 15 second and QRS 0 14 second. These tw tracings showed features of bilateral bundle-branch block in the late ntr secoid deflect ons over both right and left precordium (Lead V 0 11 second) (Lead V 0 095 second) but not in between (0 05 second in Lead V and V) also late in Lead aV (0 09 second). There were broad Q waves 0 04 to 0 05 second in Lead I II III aV and V through V ord narily h racter

istic of infarction of the anterior nd posterior w lls and, t the presence of left bundle-branch block suggest of infarction of the interventricular septum The initial notching of the S wave in Lead V and the early deep notching of S in Lead V just to the right of the transitional zone are also considered to be signs of septal or anteroseptal infarction in the presence of left bundle-branch block Electrocardiograms on May 1 2 nd 6, 1957 t cardiac rates of 85 91 and 94 also showed these changes of bilateral bundle-branch block On June 8 1957 the heart rat had increased f om 95 to 115 per minut P R w 0 15 second. There was some reduction in the oltage f QRS in 8 leads and ts duration was 0.12 second. The Q w es Lead V aV , and V through V were smaller The intrinsecoid deflection in Lead V wa less delayed— 0 08 compared to 0 095 second previously Th suggested less block in the left bundle-branch y tem w th the faster cardiac rat

Lead V and V and other lead wer taken simultaneously on a multichannel recorder on May 30 nd June 8 1957 Cardiac rates were 82 and 111 P R was 0 15 and 0 14 second The onset of QRS was synchronous or 0 005 second, or less, earlier n Lead V than in Lead V The QRS interv l wa 0.119 to 0.120 second in each lead. QRS configuration wa rR in Lead V , and QR in Lead V . The time of the intr sicoid deflection beginning f

QRS to R peak in Lead V_1, was 0.11 second, and to R peak 0.09 second in Lead V_6, and 0.05 second in Leads V and V. In Leads V_3 and V there was a deep S wave of −12 and −10.5 mm. synchronous with R in Lead V and R in Lead V_6. The late activation time over the right and left precordium but not in between was indicative of bilateral bundle branch or intraventricular block.

Discussion

The frequent occurrence of single right or left bundle-branch block makes it likely that the combination of the two—bilateral bundle-branch block—is not rare. Histologic lesions are often found in both bundles in the same individual when the electrocardiograms reveal only the pattern of single bundle-branch block.[14] Electrocardiographically the diagnosis of true bilateral bundle-branch block is made when the patterns of right and left bundle-branch block occur alternately or intermittently in the same patient together with changes in the P R interval. The QRS configuration however appears to be affected only by the side on which the blocking is greater the block on the contralateral side apparently does not affect the shape of the QRS but prolongs the A V conduction time. The intrinsicoid deflection on the side of lesser block is not delayed. This classic type of bilateral bundle-branch block has been produced experimentally.[15,16] It has been reported in human beings, but Rosenbaum and Lepeschkin[17] had been able to find in the literature only 7 proved cases of true bilateral bundle-branch block with full electrocardiographic documentation. They have discussed this Type I of bilateral bundle-branch block at length.

A second type of bilateral bundle-branch block was described by J. Marion Bryant.[18] Criteria were initial septal ventricular activation from right to left terminal activation in the right free ventricular wall and slight or greater prolongation of QRS. He observed this type of bilateral bundle-branch block also in 10 of 100 healthy young people.

A third type of bilateral bundle-branch or intraventricular block is the one with

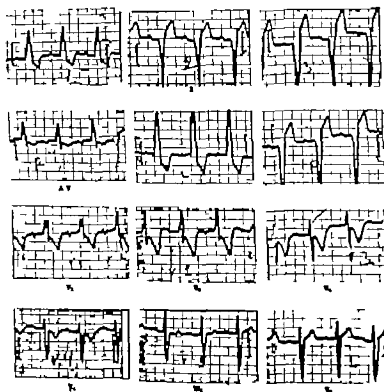


Fig. 2. Case 1. Tracings recorded 3 days after those in Fig. 1. Intrinsicoid deflection is not late in Leads V and V_6. Heart rate of 77 to 79. See text.

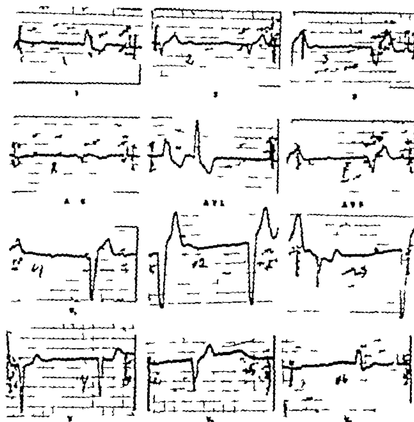


Fig. 3. Case 1. June 6, 1957. Complete trioventricular heart block.

which the present report is concerned. The electrocardiographic pattern consists of the presence of a broad QRS with the intrinsicoid deflection occurring late simultaneously over the right and left precordium but not in the intermediate area. There may be little or no increase in duration of the P-R interval. This late appearance of the intrinsicoid deflection simultaneously on the right and left sides though not in between is unusual and seemingly not in accord either with the standard theory of conduction in the bundle branch system or with vectorcardiographic principles based on the concept of a single cardiac dipole.[19] Such bilateral block may be explained by the presence of an intraventricular parietal or focal block responsible for retardation or prolongation of QRS on one or both sides (i.e., a local block in the free wall of the right or left ventricle or in both). True classic central bundle-branch block may be present in one or both ventricles, complete on one side, incomplete on one or both sides.

Parietal localization of a block which caused prolongation of QRS had been described many years ago as arborization block by Oppenheimer and Rothschild,[2] although not accepted by others.[21,22] A possible parietal localization had also been suggested by Katz.[23] More recently, Segers,[7] and Bovadjian and Van Doren[25] have described the type of block under discussion, and it has been labeled *false bilateral bundle-branch block* by Laham[25] and *doppelseitiger dilatation* by Hilmer.[26] Sanabria[27] too proposed a parietal localization for the block even in ordinary single bundle-branch block, when in a series of 6 cases he was unable to find a histologic lesion of the main bundle branches to account for the bundle-branch block. Contrariwise, Lenegre[11] had been able to show electrocardiographic and anatomic correlation in 46 cases of bundle-branch block. He was kind enough to show the slides of some of these to one of us (H. Y.). Lev and associates[29] have also found good correlation. *Mahaim fibers* have been invoked to explain *bilateral mixed block*—complete

anatomic destruction of both main bundle branches without A V block.[20] Dodge and Grant[21] suggested that in ordinary right bundle-branch block the site of the block was parietal since the initial 50 to 80 per cent of the QRS complex in peripheral leads in clinical right bundle-branch block was identical with the control QRS in his series of 80 cases each with controls. Contrariwise experimentally damage by pressure or incision distal to the main right or left bundle branch,[22] and damage by direct application of chemicals to large areas of the endocardium[22] were not able to increase the duration of the QRS interval even though the configuration of QRS was affected. In dogs, Sodi Pallares and associates[23] demonstrated total extirpation of the blocked free wall in experimental bundle-branch block without modification of the general morphology of the tracings. He stated 'The forces across the I V septum in cases of bundle branch block are very important and they give a satisfactory explanation of the unipolar morphologies. On the other hand Alzamora Castro[24] has interpreted his own experiments as favoring the concept of parietal block. He injected cocaine and other substances into a coronary artery in dogs, and thus produced focal or parietal block in the territory irrigated by the vessel into which the injection had been made with prolongation of QRS and a configuration which resembled those of incomplete and complete bundle-branch block. Peri-infarction block as described by Bayley[25] may be considered a focal parietal block. Bryant [11] too has described parietal ventricular block. This occurred in a patient during hypothermia. His illustration Figure 34 shows a late R in Lead V1 and also in Lead V Absence of intermediate leads (Leads V2 and V4) was in part a basis for criticism by Sodi Pallares who suggested that the right atrium and ventricle may have occupied the whole anterior aspect of the heart, because of

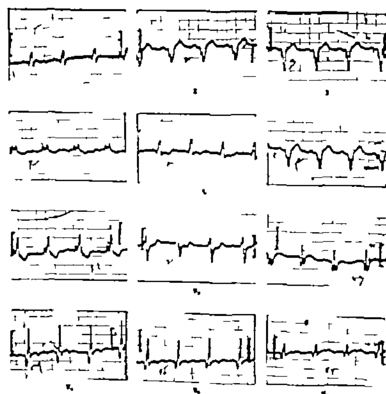


Fig. 4. Case 2. Bilateral bundle-branch block. I trinsicoid deflection is late in Leads V and V, but not in Leads V and V. See text

similarities to right atrial and right ventricular electrocardiographic morphologies.[16]

Recently by recordings of transmembrane action potential of single fibers of the bundle and of single peripheral Purkinje fibers and by use of appropriately timed extrasystoles, Hoffman and Cranefield[17] were able to demonstrate blocks peripherally at the junction of specialized fibers with the ventricular muscle cells. Whether such blocks at this site increased the duration of QRS beyond normal was not indicated. Finally Anselmi and associates[11] found that in experimental complete bundle branch blocks the contribution of the free wall of the blocked ventricle to QRS was nil. However a contribution became important in proportion to the decrease in the degree of bundle branch block and was added at the end of the septal forces in incomplete bundle branch block. Thus in spite of much evidence against a contribution of potential from the free wall of the blocked ventricle prolonging QRS in bundle-branch block especially in experimental settings, there is also considerable evidence that in certain clinical conditions and in some experiments this may occur.

The electrocardiogram of our first patient (Fig. 1) was interpreted as representing two combined bundle-branch or intraventricular blocks. One was central either complete left bundle-branch block or incomplete left bundle branch block plus a parietal left free-wall block—major because of the broad QRS 0.16 second and the more extensive changes characteristic of left bundle-branch block and temporary since 3 days afterward the intrinsicoid deflection was no longer late over the left precordium. The initial 0.04-second ventricular septal forces were directed from right to left and the absence of a Q wave in Leads I and aVL and over the left precordium were in accord with this type of block.[11] The very tall R in Lead aVL, with QRS duration greater than 0.14 second was evidence of left ventricular hypertrophy. The second block was a right bundle branch block manifest in the late R in Lead V_1 and not in Lead V_6. This block may be central and incomplete or peripheral. It was the minor block since it was found in a small area of the right precordium—only in Lead V_1 on Feb. 10 1956. It was the more persistent one. When right bundle-branch block alone was recorded (Feb. 23 1956) a broad Q wave with a notch in its descending limb was present in Leads V_1 and V_2 with cove plane T waves. This strongly suggested the presence of anteroseptal infarction evidence of which with extensive myocardial fibrosis, was found at necropsy.

In the tracing of Feb. 28 1956 the P-R interval was 0.30 second with single right bundle-branch block. On June 4 1956 complete A-V heart block was recorded with increase in the QRS interval to 0.20 second and changes in QRS contour (Fig. 3). The separate appearances of unilateral bundle-branch block of combination bundle-branch block of increasing A-V block and finally of complete A-V block with changes in QRS contour support the diagnosis of bilateral bundle branch block. Evidence of acute anteroseptal myocardial infarction and the necropsy findings of areas of fibrosis and hyalinization in the interventricular septum and ventricles suggested that at least from the time of electrocardiographic signs of bilateral bundle branch block (intrinsicoid deflection late over right and left precordium and not in between) part of the ventricular block expressed in the electrocardiogram was due to a parietal lesion—possibly peri-infarction block. The disappearance in the electrocardiogram of the left bundle branch block when the heart rate slowed was in conformity with the behavior of unstable single bundle-branch block at critical rates.[1] Segers[7] has noted the greater frequency of such intermittence in bilateral bundle branch block. Because of the presence of significant lesions in both main bundle branches intermittence might be expected to occur about twice as often in bilateral bundle-branch block as in unilateral involvement. Alternations of double bundle and single bundle-branch block he called *bloc à bascule* (seesaw). The physiologic mechanism of unstable block at a critical heart rate could apply whether the lesion was in a main bundle branch or peripherally in the Purkinje fibers or *Purkinje myocardique synapse*. The component of QRS widening if any due to left ventricular hypertrophy should be stable.[9]

In our second case the bilateral intraventricular blocks were interpreted as consisting first of a major and more permanent central right bundle-branch block, indicated by the broad QRS the initial 0.04-second ventricular septal activation from left to right, and the intrinsicoid deflection late in Lead V_1. This had been recorded singly 4 years before double bundle-branch block. The block became bilateral with the increase in QRS interval from 0.12 to 0.15 second. The time of the intrinsicoid deflection in Lead V_1 remained at 0.10 second but in Lead V_6 it increased to 0.95 second from 0.65 second. Some of this increase was due to widening of Q or QS in the left precordial leads—from 0.03 to 0.05 second in Lead V_6. The broad Q waves in Lead I and the left precordial leads, and the late R peak (0.095 second) in Lead V_6, which represented late and nearly terminal electrical forces pointing toward the anterolateral region of the left ventricle, strongly suggested the presence of peri-infarction block responsible for focal conduction delay in the anterolateral left ventricle.[30] A wide angle greater than 100 degrees was thus present between the mean initial and late QRS vector in the frontal plane an important criterion for the diagnosis of peri-infarction block.[31] The small terminal S in Lead V_6 represented late right ventricular forces due to the right bundle-branch block. R in Lead V was late in comparison to the centrally unblocked left ventricular forces. In this case a single bundle-branch block was noted at the slower cardiac rate of 60 to 70 per minute and bilateral bundle-branch block at a rate of 85 to 98 per minute. At a still faster rate, 115 there appeared to be slightly less delay over the left ventricular pathways. Significant contributions to the intraventricular conduction time due to lesions in the A-V node or common bundle of His seem unlikely because of the normal P-R interval 0.15 second. Such A-V node localization of the block may be given more consideration in our first case in which the P-R intervals were increased to 0.24 second or more. These two cases which show evidence of delay of activation over areas which correspond to the free walls of the right and left ventricles but not in between may be considered in support of the concept of focal and parietal ventricular blocks responsible for an increase in the duration of QRS with resemblance to ordinary bundle-branch block. The presence in the literature of much evidence for and against the existence of such parietal block leaves the question of its actual existence still unanswered. It should be emphasized, however that the evidence against its existence is largely experimental and in animals. Therefore the possibility of its existence in human hearts with diffuse myocardial disease and special focal myocardial pathology is not definitely excluded. Such focal parietal block could explain a component of the block in bilateral bundle-branch block of Type III.

Summary and conclusion

Three types of bilateral bundle-branch block are described. Type III is characterized by a prolonged QRS, and late intrinsicoid deflection over the right and left precordium but not in between. The mean initial 0.04-second frontal QRS vector may be directed from right to left. This type is discussed and two illustrative cases are presented one with necropsy findings. Simultaneous multilead recordings of limb and right and left precordial potentials correlated the intrinsicoid and other deflections. Changes in blocks from single to double and vice versa, *bloc à bascule* were noted with a possible critical heart rate. The mechanism of the intraventricular blocks was considered and the possibility that a focal block in the free ventricular wall caused a prolongation of QRS beyond normal was entertained. The literature on the subject pro and con was reviewed. Although there is much to support such parietal focal intraventricular block in clinical heart disease, further confirmation is desirable.

REFERENCES

1. Vesell, H. Critical rates in ventricular conduction. Unstable bundle branch block, Am. J. M. Sc. 202:198, 1941.
2. Vesell, H. Critical rates in ventricular conduction. II. Simulation of localized bundle branch block, Am. Heart J. 41:46, 1951.
3. Vesell, H. and Kraemer, L. B. Critical rates in ventricular conduction. III. Simulation of ventricular tachycardia, Am. Heart J. 41:280, 1951.

4. Vesell, H., and Friedfeld, L.: Critical rates in ventricular conduction. IV. Duration of unstable bundle branch block, Am. Heart J. 44:830, 1952.
5. Vesell, H., Tannenbaum, O., and Schack, J.: Critical rates in ventricular conduction. V. With auricular fibrillation, Proceedings of Scientific Meetings, American Heart Association, April 3, 1954, p. 63.
6. Vesell, H., and Levine, J.: Two to one bundle branch block: classification with special reference to the critical heart rate, Am. J. Cardiol. 6:963, 1960.
7. Segers, M., and Enderle, J.: Les blocs intraventriculaires bilateraux, Acta cardiol. 6:1015, 1951.
8. Nomenclature and criteria for diagnosis of diseases of the heart and blood vessels, New York, 1953, New York Heart Association.
9. Schlesinger, M. J., Zoll, P. M., and Wessler, S.: The conus artery: a third coronary artery, Am. Heart J. 38:823, 1949.
10. Wilson, F. N.: Concerning the form of the QRS deflection of the electrocardiogram in bundle branch block, J. Mt. Sinai Hosp. 8:1110, 1942.
11. Burch, G. E.: An electrocardiographic syndrome characterized by absence of Q in Leads I, V, and V_6, Am. Heart J. 51:487, 1956.
12. Chapman, M. G., and Pearce, M. L.: Electrocardiographic diagnosis of myocardial infarction in the presence of left bundle branch block, Circulation 16:558, 1957.
13. DePasquale, N., and Burch, G. E.: The spatial vector electrocardiogram in left bundle branch block and myocardial infarction, with autopsy studies, Am. J. Med. 29:633, 1960.
14. Yater, W.: Pathogenesis of bundle branch block. Review of literature, report of sixteen cases with necropsy and of six cases with detailed histologic study of the conduction system, Arch. Int. Med. 62:1, 1938.
15. Scherf, D., and Schookoff, C.: Reizleitungsstorungen im Bundel, II, Wien. Arch. inn. Med. 11:425, 1925.
16. Bernstein, W., Samet, P., and Litwak, R. S.: Experimental bilateral bundle branch block, Am. J. Cardiol. 5:799, 1960.
17. Rosenbaum, M. B., and Lepeschkin, E.: Bilateral bundle branch block, Am. Heart J. 50:31, 1955.
18. Bryant, J. M.: In Kossmann, C. E., editor: Advances in electrocardiography, New York, 1958, Grune & Stratton, Inc., pp. 163 and 173.
19. Burger, H. C.: Heart vector and leads, Am. Heart J. 61:317, 1961.
20. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic changes associated with myocardial involvement, J. A. M. A. 69:429, 1917.
21. Wilson, F. N., and Herrmann, G. R.: Bundle branch block and arborization block, Arch. Int. Med. 26:153, 1920.
22. Erickson, R. V., Scher, A. M., and Becker, R. A.: Ventricular excitation in experimental bundle branch block, Circulation Res. 5:5, 1957.
23. Rosenman, R. H., Pick, A., and Katz, L. N.: Intraventricular block, Arch. Int. Med. 86:196, 1950.
24. Boyadjian, N., and Van Doren, F.: Étude de deux cas de "bloc de branche" bilateral, Acta cardiol. 5:532, 1950.
25. Laham, J.: À propos de bloc de branche bilateral, Cardiologia 28:285, 1956.
26. Hilmer, Von W.: Die Beurteilung intraventrikularer Leitungsstorungen im Ekg, Arch. Kreislaufforsch. 33:363, 1960.
27. Sambria, T.: Contribution à l'étude anatomoclinique du bloc de branche, Acta cardiol. 5:527, 1950.
28. Lenègre, J.: Confrontation des électrocardiogrammes et des lésions histologiques du système de Tawara His dans 46 cas, Cardiologia 21, Fas. 4/5, 1952.
29. Lev, M., Unger, P. N., Lesser, M. E., and Pick, A.: Pathology of the conduction system in acquired heart disease, Am. Heart J. 61:593, 1961.
30. Mahaim, I., Winston, M. R., and Roesler, H.: Bilateral mixed block, Am. Heart J. 25:251, 1943.
31. Dodge, H. T., and Grant, R. P.: Mechanism of QRS complex prolongation in man. Right ventricular conduction defects, Am. J. Med. 21:534, 1956.
32. Erritt, R. D., Essex, H. E., and Burchell, H. B.: Studies on the spread of excitation through the ventricular myocardium, Circulation 3:418, 1951.
33. Medrano, G. A., Sodi-Pallares, D., Marsico, F., and Bisteni, A.: The importance of septal activation in the electrogenesis of the unipolar morphologies in bundle branch block, Am. Heart J. 57:126, 1959.
34. Alzamora Castro, V.: Parietal focal block: an experimental and electrocardiographic study, Circulation 7:108, 1953.
35. First, S. R., Bayley, R. H., and Bedford, D. R.: Peri-infarction block, Circulation 2:3, 1950.
36. Del Rio, R., Medrano, G., Rubio, V., Oles, J. P., Soto, J., and Sodi-Pallares, D.: Right bundle branch block with right ventricular hypertrophy, Am. J. Cardiol. 4:294, 1959.
37. Hoffman, B. F., and Cranefield, P. F.: Electrophysiology of the heart, New York, 1960, McGraw-Hill Book Company.
38. Anselmi, A., Montes, O., and Alvarez, M.: Participation of the free ventricular walls in the mechanism of production of bundle branch block, Am. Heart J. 61:357, 1961.
39. Grant, R. T., and Dodge, H. T.: Mechanisms of QRS complex prolongation in man. Left ventricular conduction disturbances, Am. J. Med. 20:834, 1956.

Tricuspid atresia
An electrocardiographic study

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The presence of left axis deviation in patients with cyanotic congenital heart disease is considered to be highly suggestive of the diagnosis of tricuspid atresia. A pattern of left ventricular predominance in precordial leads further supports this diagnosis.[1] In recent years an increased number of cases of this malformation have been reported, including a smaller but nonetheless sizable group of cases in which the electrocardiograms do not display left axis deviation. The present study attempts a reappraisal of the electrocardiographic findings in tricuspid atresia, with particular attention to the significance of normal or right axis deviation. The presence in our series of several patients who were undergoing palliative operations has also enabled us to observe some of the postoperative electrocardiographic changes in cases of this malformation.

Material and methods

The present study includes our series of 17 cases of tricuspid atresia, in which the diagnosis was verified by angiocardiography or postmortem examination, and 73 autopsied cases collected from the literature. In some sufficiently detailed information was not available for inclusion in every phase of this study, which fact accounts for the variable number of patients included in our findings. Ten of our patients had undergone operations: six of these operations were aortopulmonary anastomoses, three were subclavian-pulmonary artery anastomoses, and one was a superior vena cava–pulmonary artery anastomosis. In one patient with aortopulmonary anastomosis the atrial septal defect was enlarged at the time of a second operation.

Electrical axis was defined according to the criteria of the New York Heart Association:[2] a normal electrical axis, +30 to +90 degrees; left axis deviation, +29 to −90 degrees; and right axis deviation, +91 to +180 degrees. In a few cases collected from the literature, axis deviation was stated to be present, but the authors did not assign a numerical value to it.

The anatomic types of tricuspid atresia were subdivided according to the criteria of Edwards and Burchell, as modified by Keith, Rowe, and Vlad[3] (Table II).

Results

1. Our series. The following electrocardiographic findings were encountered in our 17 cases of tricuspid atresia (Table I).

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Table I. Summary of electrocardiographic findings and clinical and necropsy data in 17 patients with tricuspid atresia

	Axis (degrees)	P_{II} (mm.)	P-R (sec.)	Precordial pattern V1	V4	V6	$S_{V1} + R_{V5}$	Age at time of ECG	Surgery	Survival	Anatomic type
A. No axis deviation											
1. D.B.	+60	25	.10	rS	R		50	1 day	No	Died	1A
2. N.M.	+45	20	.12	rS	qR		38	2 day	No	Died	2C
3. F.B.	+35	13	.09	rS	qR		68	5 day	No	Died	1C
4. J.R.	+60	30	.12	RS	qR		44	5 day	Pott	Lived	1
	+60	40	.12	rS		qR	54	7 mo			
5. D.S.	+60	35	.12	rS	Rs		30	4 wk	No	Died	2C
6. K.B.	+50	50	.14	rS		RS	24	10 wk	Pott (6 mo.)	Lived	1
	+40	70	.16	rS		R	24	6 mo	ASD enlargement (3 yr.)		
	+40	15	.16	rS		Rs	28	4 y			
7. A.B.	+65	25	.09	rSr′	qR		26	5 mo	Pott	Lived	1
	+60	30	.11	rS		qR	52	3 y			
8. S.O.	+75	45	.10	rS		qR	26	6 mo.	Pott	Lived	1
	+70	60	.14	rS		qR	68	3 yr			
B. Left axis deviation											
9. N.G.	−25	40	.10	rS	qR		58	1 wk	No	Died	1B
10. H.J.	−30	40	.10	rS	qR		46	6 wk	No	Died	2C
11. R.Q.	−15	45	.10	rS	R		28	1 mo	Blalock	Died	2B
12. J.S.	−20	35	.09	rS	qR		28	2 mo	No	Died	1B
13. J.G.	−30	50	.11	rS	qR		52	3 mo	Pott	Lived	1
14. M.F.	−50	40	.10		Rs		26	3 mo	Pott	Lived	1
	−50	40	.12	rS	Rs		20	2 y			
15. J.W.	−60	35	.14	rS	R		62	3 y	Blalock	Lived	1
16. N.S.	−80	40	.16	R	Rs		24	3 yr	SVC-RPA anastomosis	Lived	1
	−80	30	.17	qR	Rs		24	13 yr			
17. F.S.	0	40	.16	R	qR		18	4 yr	Blalock	Lived	1

*Post-operative record.

P WAVE. A P wave which exceeded 2.5 mm. in Lead II was found in 14 patients (82 per cent) and it was considered to be peaked in at least one electrocardiogram in every case. Minor notching of this complex was present in 4 cases, with the first peak being taller in each. A diphasic P (plus-minus) was present in Lead V_1 in 14 cases. Among the 8 cases in which there were follow-up electrocardiograms for 6 months or longer prior to operation, the P wave increased in size by 1 mm. or more in 6. Initially positive P waves in Lead V_1 became diphasic in subsequent records in 2 cases. After palliative operations the P wave decreased in size by 1 mm. or more in 3 of the 7 patients in whom subsequent electrocardiograms were available, remained the same in 2, and increased in size in 2. In one of the latter patients the atrial septal defect was later enlarged surgically; after this procedure there was a 4.5-mm. decrease in the height of the P_{II} wave (Fig. 1).

P-R INTERVAL AND SEGMENT. The P-R interval was prolonged in 2 of the 17 cases (12 per cent) and measured less than 0.11 second in 4 (24 per cent). The P-R segment measured 0.04 second or less in each case with a shortened P-R interval and in 3 cases with a normal P-R interval.

AXIS QRS. Left axis deviation was present in 9 of our cases (53 per cent) and a normal electrical axis in 8; the latter will be discussed in detail subsequently. Right axis deviation was not found in our patient

Serial electrocardiograms were available over an interval of 8 months or longer in 8 patients. During the period of follow up 7 of these patients underwent anastomotic procedures. The electrical axis remained unchanged throughout the period of follow up in 6. In one patient a 35-degree shift to the left occurred preoperatively followed by a 25-degree shift to the right after subclavian-pulmonary artery anastomosis. In children this degree of change in the axis in isolated records is of dubious significance as illustrated by the other patient, whose electrical axis changed back and forth by as much as 40 degrees prior to operation (from +70 to +30 to +50 degrees in three electrocardiograms taken during a period of 3 months).

PRECORDIAL QRS. In Lead V_1 rS complexes were present in 13 cases (77 per cent). In one patient an rSr' pattern which was present at 5 months of age changed to the rS type after an aortopulmonary anastomosis 17 months later. An rSR' or RS pattern was seen in one case each and Rs was present in one patient with malrotation of the heart. In Lead V_6, qR complexes were present in 11 cases (65 per cent). Rs in 4 and R in 2. The precordial voltage criteria for left ventricular hypertrophy which were suggested by Nadas[4] to be applicable to children (S_{V_1} plus $R_{V_6} \geq 45$ mm.) were fulfilled in 9 patients.

The intrinsicoid deflection over the left precordium was delayed beyond 0.04 second in only one of our cases.

ST-T CHANGES. An upright T wave over the right precordium was found in 8 of 13 patients in whom electrocardiograms were available before 6 months of age. In only

Table II. Anatomic diagnosis and electrical axis: our series and the literature

Type	Axis	Number of cases		Ventricular septal defect		Total
		Our series	Literature†	Present	Absent	
1. With no transposition						
A. Pulmonary atresia	Left		6 (A)	2	4	6
	None	1	3 [illegible]		4	4
	Right		2 [illegible]		2	2
B. Pulmonary hypoplasia, subpulmonary stenosis	Left	2	26 (B)	24	2	28
	None		3 [illegible]	1 (small)	2	3
	Right					0
C. No pulmonary hypoplasia	Left		12 (C)	9*	2	12
	None	1		1 (absent septum)		1
	Right					0
2. With transposition						
A. Pulmonary atresia	Left		2 [illegible]	2		2
	None		1	1		1
	Right					0
B. Pulmonary or subpulmonary stenosis	Left	1	4 [illegible]	4	1	5
	None					0
	Right					0
C. Large pulmonary artery	Left	1	7 (D)	8		8
	None	2	4 [illegible]	5		6
	Right		3 [illegible]	3		3
Totals		8	73			81

*Other cases not indicated by authors.

†A = References 1, 7, 11, 13, 19. B = References 7, 18, 19, 21, 30, 31, 32. C = References 7, 12, 13, 17, 18, 25, 26, 33, 34, 35. D = References 7, 19, 21, 36, 37.

4 of these was associated flattening or inversion of the T wave present in Leads I, aVL, or V6. Fifteen patients had electrocardiograms recorded while they were not receiving digitalis: in 11 of these depression of the S-T segment and/or flattening or inversion of the T wave were present in Leads I, aVL, V5, and V6. In one patient with vertical electrical position of the heart these changes appeared in Leads II, III, and aVF. After shunt procedures the T wave became upright in Leads V5 or V6 in 4 of the 6 patients who were not receiving digitalis (Fig. 2).

2. *Factors affecting the presence of normal and right axis deviation: our series and the literature.* A total of 81 autopsied cases including 73 collected from the literature was analyzed to determine the anatomic features which affect axis deviation (Tables I and II). Left axis deviation was present in 61, normal axis in 15, and mild right axis deviation in 5. No documented case of right axis deviation of more than +110 degrees was encountered. Eight of our cases in which the diagnosis was made by angiocardiography were also included in part of the study dealing with the effects of age on axis deviation (Table III).

EFFECT OF AGE (TABLE III). Right axis deviation or a normal axis was not limited to the patients in early infancy. The average age of these patients was 8 months (range of 1 day to 5½ years) and 13 of them were over 3 months old. In serial tracings, a normal axis did not shift to the left with increasing age. Conversely, a left axis was observed frequently in the first month of life, in one case as early as 24 hours of age.

ANATOMIC SUBGROUPS (TABLE II). The majority of cases in which there was a normal axis were among those associated with pulmonic atresia (Type 1A) or transposition of the great vessels with large pulmonary artery (Type 2C) (Fig. 3). Cases of mild right axis deviation were present in either of these subgroups and in none of the others.

Three instances of normal axis were present in the cases of common type of tricuspid atresia, that associated with a normal origin of the great vessels, subpulmonic stenosis, and a hypoplastic pulmonary artery (Type 1B). The presence of an intact ventricular septum in 2 of these 3 may be significant, since in 24 of the 26 cases in this group which displayed left axis deviation a ventricular septal defect was present.

DISTRIBUTION OF AXIS IN TYPES 1A AND 2C (TABLE II). Twenty-nine cases in these subgroups were studied. Normal or right axis deviation was present in 15 (52 per cent): 10 showed no axis deviation, and in 5 there was right axis deviation.

Discussion

The characteristic electrocardiographic findings in tricuspid atresia (Fig. 4) have been described by previous authors.[4-7] The most common abnormality of the P wave is the presence of a tall, peaked P II indicative of right atrial enlargement. Minor notching of this complex and more frequently biphasic plus-minus type of P waves over the right precordium provide evidence of additional left atrial enlargement. Prolongation of the P-R interval was observed by Donzelot and co-workers[9] in 14 per cent of their cases and was present in 2 of our cases (12 per cent). Complete atrioventricular block was present in one reported case.[9] Conversely, Keith, Rowe, and Vlad[4] commented upon the absence of the P-R segment in 50 per cent of their patients, but did not include measurements of the P-R interval. This interval measured 0.11 second or less in duration in 24 per cent of our patients and was associated with QRS complexes of normal duration. A P-R segment of 0.04 second or less was present in all of our patients with shortened P-R intervals and in 3 with normal P-R intervals.

The QRS morphology in precordial leads usually reveals evidence of left ventricular predominance manifested by predominantly negative complexes over the right precordium and positive complexes over the left. Right ventricular predominance is exceptional, but in one illustrated case an Rs complex was present in Lead V4R.[10] Two other cases were described as showing right ventricular enlargement.[11,12] Right bundle branch block was present in one of our cases, and in one case reported by Chiche.[13] Equiphasic RS complexes in Lead V1 are next in frequency to the more common rS pattern seen in this lead.[4,5]

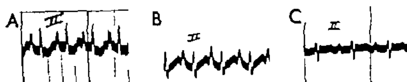


Fig. *1* Case 6, K.B. Lead II. *A* Age 5 months, before aortopulmonary anastomosis. *B* Age 2½ years, 2 years after the anastomosis. *C*, Age 4½ years, after enlargement of the atrial septal defect. Note the decreased amplitude of the P wave after enlargement of the atrial septal defect.

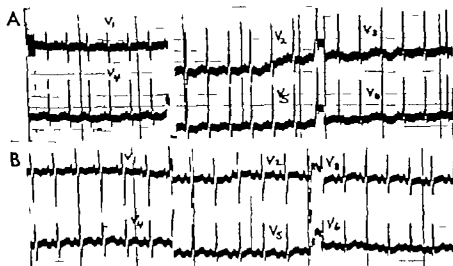


Fig. *2* Case 4. J.R. Precordial leads. *A* Age 10 days, before aortopulmonary anastomosis. *B* Age 7 months, after the anastomosis. The previously inverted T waves are upright in left precordial leads after operation.

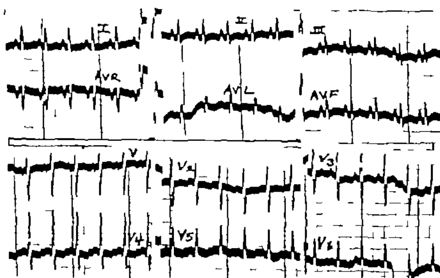


Fig. 3. Case 2, N.M. Age 2 days. ÂQRS +45 degrees. Case proved at autopsy to be Type 2C.

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tonic left ventricular hypertrophy which is invariably present.

The majority of cases in which there is a normal axis and all cases in which there is right axis deviation are associated with either pulmonic atresia or transposition of the great vessels with large pulmonary artery. These electrical axes are as common as left axis deviation among these two subgroups.

The electrical axis shows no significant change with age. Normal and mild right axis deviation is not limited to early infancy in patients with tricuspid atresia.

After successful shunting procedures the height of the P wave tends to decrease. T waves tend to become upright in left precordial leads. It is suggested that an *increase in the size of the P wave after* shunt operations should be evaluated as a criterion for enlargement of the atrial septal defect in these patients.

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REFERENCES

1. Taussig, H. B.: The clinical and pathological findings in congenital malformations of the heart due to defective development of the right ventricle associated with tricuspid atresia or hypoplasia, Bull. Johns Hopkins Hosp. 59:435, 1936.
2. Taussig, H. B.: Congenital malformations of the heart, ed. 2, Cambridge, 1960, The Commonwealth Fund—Harvard University Press.
3. Criteria Committee of The New York Heart Association: Nomenclature and criteria for diagnosis of diseases of the heart, ed. 5, New York, 1953, New York Heart Association.
4. Edwards, J. E., and Burchell, H. B.: Congenital tricuspid atresia: a classification, Med. Clin. North America 33:1177, 1949.
5. Keith, J. D., Rowe, R. D., and Vlad, P.: Heart disease in infancy and childhood, New York, 1958, The Macmillan Company.
6. Nadas, A. S.: Pediatric cardiology, Philadelphia, 1957, W. B. Saunders Company.
7. Neill, C. A., and Brink, A. J.: Left axis deviation in tricuspid atresia and single ventricle: the electrocardiogram in 36 autopsied cases, Circulation 12:612, 1955.
8. Donzelot, E., Durand, M., Metianu, C., and Vlad, P.: L'axe électrique normal ou dévié à gauche dans les cardiopathies congénitales cyanogènes. Étude de 29 cas personnels. Intérêt diagnostique, Arch. mal. coeur 43:577, 1950.
9. Dickson, R. W., and Jones, J. J.: Congenital heart block in an infant with associated multiple congenital malformations, Am. J. Dis. Child. 75:81, 1948.
10. Kreutzer, R., Caprile, J. A., Berri, G. G., and Becu, L. M.: L'électrocardiogramme dans l'atrésie tricuspidienne, Arch. mal. coeur 47:113, 1954.
11. Cooley, R. N., Sloan, R. D., Hanlon, C. R., and Bahnson, H. T.: Angiocardiography in congenital heart disease of cyanotic type. II. Observations on tricuspid stenosis or atresia with hypoplasia of the right ventricle, Radiology 54:848, 1950.
12. Blount, S. G., Ferencz, C., Friedlich, A., Mudd, J. G., Carroll, D. G., and Bing, R. J.: Physiological studies in congenital heart disease. XII. The circulatory dynamics in patients with tricuspid atresia, Bull. Johns Hopkins Hosp. 89:235, 1951.
13. Chiche, P.: Étude anatomique et clinique des atrésies tricuspidiennes, Arch. mal. coeur 45:980, 1952.
14. Portillo, B., and Anselmi, G.: Atresia tricuspidea: estudio electrocardiographico en 23 casos, Arch. Inst. cardiol. México 29:341, 1959.
15. Scott, R. S.: The correlation between the electrocardiographic patterns of ventricular hypertrophy and the anatomic findings, Circulation 21:256, 1960.
16. Rihl, J., Terplan, K., and Weiss, F.: Über einen Fall von Agenesie der Tricuspidalklappe, Med. Klin. 25:1543, 1929.
17. Bellet, S., and Stewart, H. L.: Congenital heart disease: atresia of the tricuspid orifice, Am. J. Dis. Child. 45:1247, 1933.
18. Brown, J. W., Heath, D., Morris, T. L., and Whitaker, W.: Tricuspid atresia, Brit. Heart J. 18:499, 1956.
19. Gamboa, B. M., Tell, E. H., Marino, J. J., and Davis, C. B.: Tricuspid atresia: report of 2 cases of young infants with successful operation, Am. J. Dis. Child. 78:16, 1949.
20. Sullivan, J. J., and Mangiardi, J. L.: Tricuspid atresia with right axis deviation: case report and review, Am. Heart J. 55:450, 1958.
21. Kroop, I. G., and Grishman, A.: The variability of the electrocardiogram in congenital tricuspid atresia, J. Pediat. 37:231, 1950.
22. Ebel, E. H., Lynxwiler, C. P., and Moragues, V.: Tricuspid atresia with a rudimentary right ventricle, J. Pediat. 39:211, 1951.
23. Elster, S. K.: Congenital atresia of pulmonary and tricuspid valves, Am. J. Dis. Child. 79:692, 1950.
24. Berber, S., and Salas, M.: Quoted by Sodi Pallares, D., Chavez, I., O. Zapata Diaz, J., and Velasquez, T.: Atresia pulmonar y estenosis tricuspidea sin comunicacion interventricular, Arch. Inst. cardiol. México 21:325, 1951.
25. Calleja, H. B., Hosier, D. M., and Kissane, R. W.: Congenital tricuspid stenosis: The diagnostic value of cineangiocardiography and hepatic pulse tracing, Am. J. Cardiol. 6:821, 1960.
26. Sommer, S. C., and Johnson, J. M.: Congenital tricuspid atresia, Am. Heart J. 41:130, 1951.
27. Blumenthal, S., Brahms, S., and Sussman, M. L.: Tricuspid atresia with transposition of the

great vessels successfully treated by surgery J. Mt. Sinai Hosp., New York 17:328, 1951
28. Blömer H. Zur Diagnose der Tricuspid Atresia, Ztschr. klin. Med. 151:313, 1956.
29. Rogers, H. M., Cordes, J. H. Jr. and Edwards J. E. Congenital tricuspid atresia in a boy twelve years of age, Am. J. Dis. Child. 80:427 1950
30. Bigardi, D. and Lampertico, P. Congenital atresia of the tricuspid valve. Clinical and anatomical observations apropos of a case, Minerva pediat. 11:1018 1959
31. Astley R. Oldham, J. S., and Parsons C. Congenital tricuspid atresia, Brit. Heart J. 15:287 1953.
32. Gasul A. L., and Montero, E. S. Tricuspid atresia Brit. M. J. 2:No 5056, 1283 1957
33. Pearson H. A. and Cone T. E. Jr. Harlequin color change in a young infant with tricuspid atresia, J. Pediat. 50:609 1957
34. Miale, J. B., Millard, A. L., Beno T. J. and Custer G. S. Congenital tricuspid atresia associated with interauricular and interventricular septal defects, Am. Heart J. 36:438 1948
35. Schaede, A. Die Tricuspidalatresie Deutsches Arch. klin. Med. 199:102 195
36. Ohanessian, O. D., and Rodriquez, M. B. Congenital tricuspid atresia report of two cases A.M.A. Arch. Path. 67:439 1959
37. Robinson, A., and Howard, J. E. Atresia of the tricuspid valve with transposition of the great vessels, Am. J. Dis. Child. 75:5 5 1948

Sequential changes in the development of the electrocardiographic pattern of left ventricular hypertrophy in hypertensive heart disease

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Although recent reviews[1-3] have summarized the available data concerning the diagnostic value of the electrocardiogram in left ventricular hypertrophy, little attention has been directed toward the sequential changes in the development of this pattern. Much of the controversy concerning the significance of the electrocardiographic pattern of left ventricular hypertrophy has centered upon the interpretation of ST-T changes. The problem of long standing[4-8] is whether the ST-T abnormalities are purely secondary to the increasing magnitude of the QRS vector or whether they represent an additional complication. Adequate analysis of these relationships would be enhanced by clinical electrocardiographic correlations over the entire lifespan of developing hypertrophy. Long-range electrocardiographic studies have been hampered since routine precordial leads have only been available since 1945. The present material consists of such studies of developing hypertrophy in 22 patients.

Material and methods

The material consists of 9 patients from the Los Angeles County Hospital and 13 private patients. The patients from the Los Angeles County Hospital were those who died between 1950-1960 with a clinical diagnosis of hypertensive heart disease; their records had to contain both a normal control electrocardiogram and subsequent abnormal electrocardiogram, including one taken within 6 months of death. The private patients were those with a clinical diagnosis of hypertensive heart disease who were followed for at least 5 years and who showed progressive electrocardiographic changes after having started with a normal pattern. This selection insured the presence of both ambulatory and seriously ill patients in the study. Patients with a clearly documented history of myocardial infarction were excluded. The usual measurements of QRS, T, and the Q-T interval were made, and in addition special attention was given to the position of the "J point" in reference to the P-Q level. From these measurements the Lewis index[9] $(R_1 + S_3) - (R_3 + S_1)$, the Sokolow index[10] $(R_{V5} + S_{V1})$, the R/T ratio in Lead V_6,[1] and the difference between the height of T_3 and the height of T_1,[11] hereafter called the "T_3-T_1" index," were calculated. A Lewis index greater than 18, a Sokolow index greater than 35, an R/T ratio in Lead V_6 greater than 10, and a

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*Table I Group A**

Patient	Time†	Blood pressure (mm. Hg)	Indices			T	R/T in V	"J point"	Q-T	Remarks
			Lewis	T_I-T	Sokolow					
1. N.J. F 62	0	220/130	19.0	−2.0	29	+2.0	10.0	Iso.	42	
	30	220/130	23.0	−1.0	20	+2.0	5.5	Iso.	46	
	82	220/130	16.0	−1.0	33	+2.0	9.5	−0.25	46	
	99	220/130	19.0	−1.0	41	+1.0	22.0	−0.50	46	HBP 8 yr
2. M.L. F 61	0	230/120	20.0	−2.0	27	+2.0	6.5	Iso.	46	
	52	230/120	23.0	−2.0	29	+1.5	8.5	Iso.	46	
	61	230/120	21.0	−2.0	36	+2.5	9.0	−0.50	44	
	64	230/120	25.0	−2.0	41	+2.5	11.0	−1.00	44	
	72	220/120	25.0	−2.0	41	+2.5	11.0	−0.50	48	HBP 12 yr
3. M.O. M, 73	0	160/90	2.0	0	26	+2.0	8.0	Iso.	41	Digitalis
	24	200/100	5.0	−1.5	31	+1.0	22.0	Iso.	40	
	30	200/100	5.0	−1.5	31	+1.0	22.0	−0.50	46	
	71	200/110	4.5	0.	31	+0.5	21.0	−1.00	46	
	85	240/120	10.0	−1.0	42	+1.0	29.0	−0.50	40	HBP 17 yr
4. J.H. M 62	0	190/130	14.0	0.	22	+2.0	4.0	Iso	40	Angina
	9	220/120	14.0	0.	27	+1.5	8.0	−0.50	44	Digitalis
	25	200/110	11.5	0.	33	+0.5	28.0	−1.00	44	HBP 7 yr
5. N.M. M 54	0	170/100	3.0	+0.5	21	+0.5	9.0	Iso.	.52	Digitalis
	24	130/100	15.0	+0.5	28	+1.0	13.0	−0.50	.38	Digitalis, HBP 5 yr
6. W.Mc. M 43	0	220/110	14.5	−2.5	40	+2.5	10.0	Iso	40	
	82	200/100	21.0	−1.0	30	+0.5	32.0	Iso.	40	
	88	200/100	21.0	−2.5	34	+0.5	32.0	Iso.	40	
	118	200/100	21.0	−2.5	34	+0.5	32.0	Iso.	40	HBP 15 yr
7. A.F. F 69	0	240/120	10.0	−2.0	30	+4.0	4.3	Iso	.36	
	43	240/120	3.0	−1.5	43	+2.0	12.8	−1.00	36	
	60	240/120	−2.0	−1.0	48	+3.0	8.3	−2.00	42	HBP 31 yr
8. R.O. F 35	0	170/115	7.0	−3.0	34	+1.5	11.0	Iso.	35	
	9	170/115	9.0	−2.0	45	+2.0	11.0	Iso.	40	
	15	170/115	11.0	−1.5	51	+2.0	8.5	−1.00	46	
	34	140/85	9.0	+0.5	62	+2.0	13.8	−1.50	48	
	46	140/90	12.0	−2.0	42	+3.5	6.4	−0.50	.50	HBP 4½ yr

*All values in boldface are abnormal.
†Months from first tracing.
Iso: Isoelectric; HBP: Duration of hypertension.

$T_I - T_1$ index greater than 0 were considered to be abnormal. When T_{V_1} became flat or inverted the R/T ratio was called "infinity." Changes in the Lewis index and the $T_I - T_1$ index represented *shifts in the* frontal plane vector and changes in the Sokolow index and R/T ratio represented shifts in the horizontal plane vector. The 22 patients were divided into three groups. Group A consisted of 8 patients who showed progressive increases in the height of QRS with minimal changes in the T wave. Group B included 8 patients who showed a progressive increase in the height of R and a concomitant decrease in the height of T with the eventual flattening or inversion of T. Group C consisted of 6 patients whose sequential changes were interrupted by marked alterations in ST-T with relatively little progression in QRS.

*Table II Group B**

Patient	Time†	Blood pressure (mm Hg)	Indices: Lewis	Indices: T_I-T	Indices: Sokolow	Tv	R/T in V_5	J point*	Q-T	Remarks
1 M.S. M 67	0	170/100	11.0	0	26	+2.5	8.7	−0.25	—	
	72	210/110	**20.5**	+1.0	**35**	**Flat**	**Inf**	−0.50	—	
	96	130/80	15.5	+1.5	11	**−2.0**	**Inf**	−0.50	—	
	98	180/90	16.5	**+3.5**	31	**−3.0**	**Inf**	−3.00	—	Digitalis HBP 8 yr
2 I.G. F 64	0	240/140	2.0	−4.0	30	+4.0	4.0	Iso.	.38	Digitalis and angina
	19	230/120	2.0	−3.0	30	+4.0	4.0	−1.00	.46	
	48	240/130	2.0	−3.0	30	+4.0	3.3	Iso.	.39	
	72	220/110	4.0	−1.0	36	+3.0	6.0	−1.00	.36	Digitalis and angina
	73	220/110	4.0	0	**45**	**Flat**	**Inf**	−0.75	.40	HBP 10 yr
3 J.Mc. M 53	0	180/90	12.0	−1.0	37	+2.0	8.5	−0.50	.48	
	12	170/90	14.0	0	**51**	+1.0	**23.0**	−0.50	.48	
	28	210/100	11.0	+1.0	**51**	+1.0	**21.0**	−0.50	.48	
	45	200/100	9.0	**+3.0**	**51**	+1.0	**22.0**	−1.00	.48	
	51	200/100	9.0	**+3.0**	**51**	+1.0	**22.0**	−0.50	.44	Digitalis HBP 17 yr
4 M.C. F 56	0	170/30	16.0	−3.0	—	—	2.0	Iso.	.46	Digitalis and angina
	24	165/100	16.0	−3.0	—	—	—	Iso.	.46	
	120	235/110	**21.0**	−2.5	32	+2.5	3.3	−0.50	.38	
	122	210/120	**29.0**	−4.5	14	+3.0	2.7	−0.75	.48	No digitalis
	130	200/100		−2.0	29	0	4.3	−0.5	.40	
	132	200/90	**32.0**	0	12	0	Inf	−1.0	.37	HBP 6 yr
5 L.M.R. F 67	0	210/90	13.0	0	30	+1.0	**20.0**	Iso.	.46	
	60	170/96	11.0	**+2.0**	16	−1.0	Inf	−0.75	.40	HBP 5 yr
6 A.C. F 63	0	205/110	2.0	**+1.0**	14	+3.0	4.0	Iso.	.30	
	48	150/80	6.0	**+2.5**	**42**	[illegible]	Inf	−0.50	.46	HBP 12 yr
7 R.S. F 79	0	185/100	6.0	−0.5	27	+1.5	7.5	Iso.	.46	Angina
	24	200/100	10.0	+0.5	40	+1.0	1 .0	Iso.	.40	
	48	170/80	**20.0**	**+2.0**	**35**	+0.5	**26.0**	−0.50	.44	
	60	170/100	1 .0	+1.0	[illegible]	Flat	Inf	Iso.	.46	HBP 5 yr
8 S.S. F 40	0	155/100	11.0	−5.0	28	+1.5	6.0	Iso.	.42	
	120	260/150	**36.0**	**+6.0**	**53**	**−6.0**	**Inf**	−1.5	.36	HBP 10 yr

*All values in boldface are abnormal.
†Months from first tracing.
Iso: Isoelectric. Inf: Infinity. HBP: Duration of hypertension.

Results

There were 8 patients in Group A (see Table I) selected on the basis of incremental changes in the Sokolow index with minimal changes in the T wave. Six patients showed stepwise increases in the Sokolow index. In one patient (W. Mc.) who was on pentolinium the index decreased despite a constant blood pressure and in a 35-year-old woman (R.O.) the index varied with the level of blood pressure. The Lewis index reached an abnormal level in only 3 patients. T_{V5} showed little over-all change, the greatest decrease from the first to the last tracing was 2 mm. The initial height of T_{V5} was rarely greater than 2.5 mm. Changes in the frontal plane T vector (the $T_3 - T_1$ index) were less than in the precordial leads. The R/T ratios in Lead V_5 all became abnormal, reflecting the increasing height of R_{V5} in the presence of minimal changes in T_{V5}. The J point became depressed in 7 cases. The Q-T interval tended to increase slightly. Serial

electrocardiograms of a typical patient are shown in Fig. 1 Five of the 8 patients are still asymptomatic after 10 8 7 6, and 3 years of observation with known hypertension of 5 to 17 years. Two patients (J H and N M) died after 2 and after 3 years of observation One patient (J H) had angina pectoris. There was only one patient (N M) from the Los Angeles County Hospital in this group

There were 8 patients in Group B (see Table II) the group in which gradual or incremental changes in the QRS indices were accompanied by progressive decreases in the height of T wave, with the eventual flattening and inversion of the T wave The general range of the QRS indices was the same as in Group A although occasionally there were abrupt shifts. As in the previous group the Lewis index was less informative The total changes in T_{V_6} were in the range of 4 to 6 mm For example in one patient (M Y) T_{V_6} was +2.5 mm at the start and changed to −3 mm in the last tracing representing a total change of 5.5 mm In 2 patients (J Mc. and R.S) the T_1-T_1 index showed a more significant change than the T_{V_6} measurements. R T ratios became abnormal in every case Changes in the "J point" were more pronounced than those in Group A. Serial electrocardiograms of a typical patient are shown in Fig 2 Six patients in this group were from the Los Angeles County Hospital and therefore were selected on the basis of death from

*Table III Group C**

Patient	T mo†	Blood pressure (mm. Hg)	Indices: Lewis	Indices: T_1-T	Indices: Sokolow	T_{V_6}	R/T in V	J point"	Q-T	Remarks
1 H.G.	0	170/90	3.5	+2.0	9	+0.5	10.0	−1.00	.40	Angina
M, 43	32	170/90	2.5	+1.5	35	+2.0	10 0	−0 50	.36	
	60	200/100	9.5	0	30	−3.0	Inf.	−2.00	.40	
	72	200/100	7 0	0	30	−2.0	Inf	−1.20	.38	No angina HBP 6 yr
2 J W	0	150/110	0	0	32	+3.0	5.0	Iso.	.42	
M, 49	36	170/100	3.0	+1.0	37	−4.0	Inf.	−0.50	.43	
	42	175/110	1.0	+1.0	43	−3.0	Inf.	−0.50	.44	
3. L.R.	0	200/100	15.0	+0.5	20	+2.0	3 0	Iso	.38	Digitalis
F 75	9	260/100	8 0	+0.5	39	+2.5	6 0	−0.50	.38	
	83	220/120	13.0	+3.0	34	−1.5	Inf	−2.00	.42	Angina
	101	220/120	13.0	+2.0	33	+1 5	6 0	−1 00	.46	HBP 15 yr
4 H.S.	0	160/90	12.0	0	19	+3.0	3 0	Iso.	.42	
M 62	12	160/90	11.0	−0.5	26	+5.0	3 0	Iso.	.40	
	36	160/90	11.0	−0.5	26	+5.0	3.0	−0.50	.40	
	72	190/110	15 0	+3.0	36	−5.0	Inf	−2.50	.50	HBP 6 yr
5 C K.	0	130/90	10 0	−.5	25	+1.5	5.0	−0 50	.36	
M 38	8	200/100	9.0	−1.5	25	−1.0	Inf	−0.25	.35	Digitalis
	20	200/100	8 0	−1.0	30	−1.0	Inf	Iso	.36	Angina
	27	200/100	9.0	−2.0	33	−2.0	Inf.	−0 50	.32	
	39	170/90	6 0	−0.5	28	−0.5	Inf	−0.50	.33	Angina HBP 3 yr
6. W.L.	0	180/110	3.0	−1.0	34	+2.0	8.0	Iso	.36	
F 48	9	180/110	8 0	−3 0	35	−2.0	Inf	−0 25	.46	Angina
	10	220/120	11.0	−5.0	40	Flat	Inf	−0 50	.36	
	11	220/140	11.0	−2.5	27	+2.0	6 0	−0 50	.38	

*All values in boldface are abnormal
†Months from first tracing
Iso: Isoelectric. Inf.: Infinity. HBP: Duration of hypertension.

eral electrocardiographic features of this group are not different from those of Group A save in the direction of T. The voltage of QRS, the depression of the J point, and the length of the Q-T intervals were not significantly different in the two groups.

The problem then is to consider what possible clinical differences distinguish the patients of Group A with upright T waves from the patients of Group B with flat or inverted T waves. Schröder and Sumrua truamphol[16] found ST-T changes in 84 per cent of hypertensive patients with decompensation, whereas only 8 per cent of the hypertensive patients without decompensation showed similar changes. This led them to conclude that the electrocardiographic changes were due to injury of the left ventricular wall and not to left ventricular hypertrophy alone. Mackerson[17] noted that over 60 per cent of patients with hypertensive heart failure had ischemia of the coronary artery as an apparent precipitating factor in the failure.

The data of Perera[18] may also be pertinent; he showed that in hypertensive patients followed over a 10-year period those with electrocardiographic damage and those with angina pectoris both had the same limited survival period of 5 years.

The above-cited authors have presented evidence to suggest that some of the electrocardiographic patterns of left ventricular hypertrophy may be due to the presence of chronic insufficiency of the coronary artery. On the other hand, postsympathectomy studies such as those of Bridges and associates,[19] and studies of the effects of antihypertensive medication, such as those of Helmcke and associates,[20] have emphasized the early reversibility of ST-T changes, evidence which is inconsistent with the view that chronic changes in the coronary artery are permanent. Recently, Georgopoulos and associates[21] have emphasized not only the reversibility of ST but also noted that a decrease in the voltage of R might occur at the time of acute lowering of blood pressure with intravenous sodium nitroprusside. Smirk[22] has found a definitive lowering of R waves to a normal level after effective treatment with hypotensive agents, even though subsequent autopsy findings demonstrate the persistence of left ventricular hypertrophy.

In our Group C there is little doubt that episodes of acute insufficiency of the coronary artery have been superimposed on the underlying left ventricular hypertrophy. The electrocardiographic patterns in this group show more obvious bowing and deeper T-wave inversion (see Fig. 3). In a comparison of sequential tracings a marked change in T occurs with minimal alterations in the voltage of QRS. These disproportionate changes distinguish patients of this group from those of Group B.

The ST-T changes of acute insufficiency of the coronary artery must be recognized as such, being independent from the underlying pattern of hypertrophy. The spontaneous reversibility of these ST-T changes may be wrongly attributed to the effects of antihypertensive therapy. The position of the J point tended to distinguish coronary changes in the hypertensive patient from the changes in uncomplicated coronary artery disease. In a prior study (unpublished observations[23]) the J point was found to be uniformly elevated in coronary artery disease and depressed in left ventricular hypertrophy.

Conclusions

1. The electrocardiographic pattern of left ventricular hypertrophy in hypertensive heart disease consists of sequential stepwise increases in the voltage of QRS recorded primarily in the horizontal plane.

2. Three separate groups of patients were described. In the first group QRS changes were dominant and T-wave changes were always minimal. In the second group, increases in QRS voltage were accompanied by ST-T changes which progressed to the flattening and inversion of the T wave.

3. A third group was described in which changes in ST-T were disproportionate to incremental changes in QRS.

4. It would appear that the three groups as described represent (a) pure work hypertrophy, (b) work hypertrophy sufficient to produce relative insufficiency of the coronary artery, and (c) distinct acute changes in the coronary artery which are superimposed upon the pattern of left ventricular hypertrophy.

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REFERENCES

1. Griep, A. H. Pitfalls in the electrocardiographic diagnosis of left ventricular hypertrophy: a correlative study of 200 autopsied patients, Circulation 20:30, 1959.
2. Scott, R. C. The correlation between the electrocardiographic patterns of ventricular hypertrophy and the anatomic findings, Circulation 21:256, 1960.
3. Selzer A., Ebnother C. L., Packard P., Stone A. O., and Quinn, J. E. The reliability of the electrocardiographic diagnosis of left ventricular hypertrophy, Circulation 17:255, 1958.
4. Symons, C., and Wahl, E. The electrocardiographic diagnosis of left ventricular hypertrophy in hypertension, Brit. Heart J. 23:208, 1961.
5. Simpson, F. O.: Electrocardiographic signs of left ventricular hypertrophy and strain in hypertensive patients, Brit. Heart J. 22:227, 1960.
6. Katz, L. N. Electrocardiography, ed. 1, Philadelphia, 1941, Lea & Febiger.
7. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Hecht, H., Cotrim, N., Barker, P. S., Scarsi, R., and Menezes de Oliveira, R. The precordial electrocardiogram, Transactions of the Association of Life Insurance Medical Directors of America, 53rd Annual Meeting, H. E. Ungerleider, editor, New York, 1943, p. 154.
8. Sodi-Pallares, D., and Calder, R. M. New bases of electrocardiography, St. Louis, 1956, The C. V. Mosby Company.
9. Lewis, T. Observations upon ventricular hypertrophy with especial reference to preponderance of one or other chamber, Heart 5:367, 1914.
10. Sokolow, M., and Lyon, T.: The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads, Am. Heart J. 37:161, 1949.
11. Ashman, R., and Hull, E. Essentials of electrocardiography, New York, 1947, The Macmillan Company.
12. Barnes, A. R., and Whitten, M. B. T wave negativity in predominantly left ventricular strain, Am. Heart J. 5:14, 1929.
13. Winsor, T., and Beckner, G. Hypertrophy of the heart: electrocardiographic distinction between physiologic and pathologic enlargement, California Med. 82:151, 1955.
14. Grubschmidt, H. A., and Sokolow, M. The reliability of high voltage of the QRS complex as a diagnostic sign of left ventricular hypertrophy in adults, Am. Heart J. 54:689, 1957.
15. Sokolow, M., and Sanazaro, P. J. Cardiovascular disease: arterial hypertension, Annual Review of Medicine 11:59, 1960.
16. Schröder, R., and Sumrnatrusmphol, N. Die Erregungsrückbildung in EKG bei linkshypertrophie des Herzens, Ztschr. Kreislaufforsch 48:626, 1959.
17. Mickerson, J. N. Heart failure in patients with high blood pressure, Brit. Heart J. 21:218, 1959.
18. Perera, G. A. Hypertensive vascular disease: description and natural history, J. Chron. Dis. 1:33, 1955.
19. Bridges, W. C., Johnson, A. L., Smithwick, R. H., and White, P. D. Electrocardiography in hypertension: a study of patients subjected to lumbodorsal splanchnicectomy, J.A.M.A. 131:1476, 1946.
20. Heinecke, J. G., Schneckloth, H. R., and Corcoran, A. C. Electrocardiographic changes of left ventricular hypertrophy: effects of antihypertensive treatment, Am. Heart J. 53:549, 1957.
21. Georgopoulos, A. J., Vlastaris, P. A., and Proudfit, W. L. R wave voltage changes in relation to arterial pressure in hypertensive patients, Cleveland Clin. Quart. 28:46, 1961.
22. Smirk, F. H. Personal communication.
23. Cosby, R. S., and Herman, L. M. Unpublished observations.

The hemodynamics in labile hypertension

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The problem of evaluating the patient who presents with an elevated blood pressure is a common and yet difficult one. Although not conclusive, the work of Pickering and his associates[1] has suggested that blood pressure describes a continuous frequency distribution and that no sharp separation into hypertensive and normotensive class is evident. This lack of a satisfactory definition of the separation between a normal and an abnormal blood pressure as well as the lack of any adequate prognostic test makes the evaluation of the significance of an elevated blood pressure in any one patient extremely uncertain. It is often necessary to follow the patient for an extended period of time before hypertension and hypertensive vascular disease can be documented.[2] If there were an adequate prognostic test, the patient who might be expected to develop the complications of hypertension could be selected in advance and possibly by treatment such complications could be prevented.

Preliminary work in this laboratory had suggested that the measurement of hemodynamics might have value as such a test to separate those who are more likely to develop fixed hypertension and hypertensive vascular disease. Further work which has expanded the study to include 52 subjects under 50 years of age and an additional 21 subjects over this age has been carried out, and the results appear to bear out the original suggestion and to be worth reporting at this time.

Materials and methods

In order to collect a reproducible group of subjects who were early in the disease and who did not already have fixed essential hypertension, the study was limited to hospitalized patients who were hypertensive on admission but who had at least one casual blood pressure reading in the normal range during the first 3 days in the hospital. The upper limit of normal was taken to be 150/90 mm. Hg for those under 30 years of age and 150/100 mm. Hg for those above this age. No patient was included in the study if he had a history of renal disease, angina, previous myocardial infarction, or cerebral vascular accident. Likewise, only one patient (in the high cardiac index group over age 50) was included with eye grounds over Grade II of Keith, Wagener, and Barker.

A total of 52 subjects who were under 50 years of age and 21 who were over this age were studied. For comparison a group

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of 28 hospitalized subjects under 50 years of age and 13 over this age who had normal blood pressures and were without evidence of cardiovascular disease were studied The majority came from the general medical wards of a Veterans Administration Hospital and because of this fact male subjects predominate in the study About one half of the patients were referred to us for study because of their elevated blood pressure, and the other half were selected through a review of the charts on the hospital wards. All subjects had a routine work up including a complete history and physical examination complete blood count urinalysis, determination of non protein nitrogen chest x ray film and 12 lead electrocardiogram

Every effort was made to standardize the study procedure from patient to patient so that results could be compared. The patient was seen the day prior to the test, and the procedure was explained to him. At that time a brief history of the pertinent points was taken and a physical examination was made by one of us. After a light breakfast the patient was brought to the cardiovascular laboratory and under local anesthesia a No 18 gauge Cournand needle was introduced into the right brachial artery and a No 18 gauge intravenous needle into the left antecubital vein. The latter was kept open with a slow drip of 5 per cent glucose in water to which 25 mg of heparin had been added Then the patient rested in the supine position for 20 minutes or until the blood pressure, which was recorded by the auscultatory method every 2 minutes, was stable and the pulse was under 100 The first cardiac output was then determined and after the patient had rested for an additional 10 minutes, the determination of output was repeated.

The cardiac outputs were determined by the dye-dilution method of Hamilton and Stewart using the interrupted sample technique and radioactive iodinated human serum albumin as the indicator To insure as complete and instantaneous mixing of the indicator as possible, a polyethylene tube which had a capacity of 3 c.c. was attached to the venous needle. This was filled with the indicator 20 microcuries in 0 8 c.c. of saline, through one arm of a three way stopcock. The arm was turned and the contents of the tube rinsed into the vein with a 20-c.c. saline rinse. Simultaneously with the injection interrupted samples were collected from the brachial artery at 2-second intervals for 44 seconds. These were collected by allowing the blood to flow through a polyethylene tube which had a capacity of 1.8 c.c. (i d of 3.5 mm. and length of 20 cm.) into 2-c.c. tubes which had been previously wet with heparin From each tube 0.5 c.c was pipetted into distilled water and counted in a well counter The results were plotted on semi-logarithmic paper and the downslope was extrapolated to 5 per cent of the peak concentration then the curve was replotted on linear graph paper The mean concentration was then determined by planimetric measurement of the linear dye curve. Cardiac output was calculated from the Stewart formula

$$\text{COP (liters/min.)} = \frac{I\ 60}{\bar{c}\ t}$$

where I = the amount injected in counts per minute $\bar{c}$ = the mean concentration of the dye during the initial circulation in counts per minute per liter and t = the time of the single circulation. Immediately after the determination of output the blood pressure and pulse were taken and the total peripheral resistance was calculated from formula (1) (*below*) and the mean blood pressure was determined by formula (2) (*below*)

In 11 of the subjects, arterial and venous blood catecholamines were measured at the time of the hemodynamic study These

$$(1)\ \text{Total peripheral resistance (dynes cm.}^{-5}\text{ sec.)} = \frac{\text{Mean blood pressure}}{\text{Cardiac output (c.c./sec.)}} \times 1{,}332$$

$$(2)\ \text{Mean blood pressure} = 1/3\ \text{pulse pressure} + \text{diastolic pressure}$$

Table I Hemodynamics in labile hypertension

Number	Blood pressure on admission	Pulse on admission	Blood pressure range	Pulse COP	Stroke volume (c.c.)	Blood pressure with COP	Cardiac index (L./min./M^2)	Resistance (dynes cm.$^{-5}$ sec.)
				Subject with labile hypertension under age 50				
High cardiac index (21)	169/104	88	174/107 127/77	90	121 ± 29	156/96 157/104	5 72 ± 0 99 (I) 4 88 ± 0 58 (II)	867 ± 209 (I) 1 028 ± 241 (II)
Normal cardiac index (31)	174/112	86	175/113– 122/77	78	92 ± 20	140/93	3 71 ± 0.61	1,278 ± 355
Normal subjects (28)						118/74	3 73 ± 0.52	1,018 ± 997
				Subject with labile hypertension over age 50				
High cardiac index (6)	199/113	85	191/110– 131/78	79	127	158/92	5.34 ± 0.47 (I) 4.27 (II)	929 ± 168
Normal cardiac index (15)	198/114	86	180/109– 129/81	79	86	157/96 144/89	3.64 ± 0.32 (I) 4 01 ± 0 95 (II)	1 427 ± 233 (I) 1,290 ± 359 (II)
Normal subjects (13)						133/83	3.61 ± 0 75	1,338 ± 300

were determined by the method of Von Euler as modified by Cohen.[8] Thirty cubic centimeters of blood were drawn into a heparinized syringe and placed at once in an iced centrifuge tube. At the end of the procedure these were centrifuged, the pH adjusted, and the catecholamines adsorbed on to alumina. This was passed through a chromatographic column and after being eluted the catecholamines were oxidized using potassium ferricyanide. The samples were read against standard solutions in an Aminco Bowman spectrophotofluorometer. The mean recoveries with this technique were 93 ± 14 per cent for norepinephrine and 92 ± 11 per cent for epinephrine using concentrations of cathecholamines of 5 to 10γ per liter.

Results

The results of the hemodynamic studies are summarized in Table I. For the 28 normal subjects who were under 50 years of age (mean age of 34) the mean cardiac index was 3 73 L./min./M^2 (S.D. ± .52) and the total peripheral resistance was 1 018 dynes cm.$^{-5}$ sec. (S.D. ± 100). In the 13 subjects who were over 50 years of age (mean age of 57) the cardiac index was 3 61 L./min./M^2 (S.D. ± .75) and the total peripheral resistance was somewhat higher 1,338 dynes cm.$^{-5}$ sec. (S.D. ± 300). In the normal subjects the cardiac index was reproducible with a coefficient of variation of 12 per cent over a 10-minute period, whereas that for total peripheral resistance was 8 per cent.

Using a cardiac index of 4 77 L./min./M^2 as a dividing line, arbitrarily chosen as 2 standard deviations above the normal level, we could divide the hypertensive subjects into two groups; the results are summarized in Table I. In those with a normal cardiac index, approximately two thirds of the group, the total peripheral resistance was somewhat elevated, 1,278 dynes cm.$^{-5}$ sec. for those under 50 years of age, and 1 427 dynes cm.$^{-5}$ sec. for those over 50 years of age. In the subjects with an elevated cardiac index, in spite of the fact that approximately one half of them were hypertensive at the time of the study, the calculated total peripheral resistance was lower than in the normal subjects for those under

age 50 it was 867 dynes cm $^{-5}$ sec with a cardiac index of 5.72 and for those over the age of 50 it was 929 dynes cm $^{-5}$ sec. with a cardiac index of 5.34. In the under 50 age group the differences between the cardiac index and total peripheral resistance for the two groups are statistically significant with a p value of less than 0.001. Likewise, the differences between the cardiac index for the normal subjects under 50 years of age and the high-output hypertensive subjects are significant, with a p value of less than 0.001. Because of the small number in the group over age 50 a statistical analysis was not made.

Thus approximately one third of the subjects with an initially elevated blood pressure showed a hemodynamic pattern which is different from the one usually seen in essential hypertension, i.e., a normal cardiac index and an elevated total peripheral resistance.[4] The high-output pattern was not limited to those under age 50; it occurred also in 6 of the 21 subjects who were over that age. The differences in cardiac index were not due to rate alone since the stroke volume was elevated in the group with the high output; for the group under 50 it was 121 c.c. as compared to 90 c.c. (p less than 0.005) and in those over 50 it was 12 c.c. as compared to 86 c.c.

The two different hemodynamic patterns are not completely separate, as can be seen by the standard deviation for each group. For both age groups the complete separation between the two patterns for cardiac index is of course arbitrary, whereas for total peripheral resistance there is some overlap. The explanation for this is that, in part at least, not all of the subjects had an elevated blood pressure in either group at the time of the study. In those under 50 years of age, 12 of the group with a high cardiac index were hypertensive and 12 of those with a normal index, and for those over 50 years of age there were 4 and 8, respectively. On the basis of blood pressure there was no separation between the groups.

The reproducibility of the hemodynamic pattern was studied at 10-minute intervals, day to day on the same admission, and from admission to admission. The 10-minute reproducibility is shown in Table I. For those under age 50 only in the group with a high cardiac index were there enough determinations to be meaningful. In the 8 subjects, only one showed a fall in the cardiac index below 4.35 L./min./M.²; the mean change in cardiac index for the entire groups was 5.72 to 4.88 L./min./M.², and the mean change in total peripheral resistance was 867 to 1,028 dynes cm $^{-5}$ sec. In the 3 patients over age 50 with an elevated cardiac index who were studied at a 10-minute interval, the cardiac index fell below 4.7 L./min./M.² in one. In those with a normal cardiac index the mean cardiac index rose from 3.64 to 4.01 L./min./M.², and the resistance fell from 1,427 to 1,290 dynes cm $^{-5}$ sec. For only 1 of 6 did the cardiac index increase above 4.12 L./min./M.²

The day-to-day and admission-to-admission reproducibility is shown in Tables II and III. In the repeat study which was made on 2 subsequent days, 12 patients were studied. In one of the 4 with an initially elevated cardiac index the repeat study on the second day gave findings that were within the normal range, and in 3 of the 8 who initially had a normal cardiac index, the index rose on the second day to above normal. For the repeat study on two separate admissions, 3 patients (I. H., F. S., and G. M.) were not hypertensive on one of the two admissions but, when hypertensive, they had a high cardiac index and lower resistance than when normotensive. Only 1 patient changed his classification between the two studies, Subject No. 14, and interestingly he was less hypertensive on the admission when the cardiac index was lower.

The results of the measurements of cathecholamines in the two groups are shown in Table IV. For the subjects with normal cardiac index and high total peripheral resistance the mean arterial and venous norepinephrine was slightly elevated, but the differences were not statistically significant. Likewise, because of the large number without measurable levels there is no correlation between the level of the total peripheral resistance and the level of norepinephrine or epinephrine.

The clinical characteristics of the two groups are summarized in Table V. In the under 50 group, those with a high cardiac

Table II Reproducibility of the hemodynamic pattern day to day

Subject number	Cardiac index		Blood pressure		Resistance	
	I	II	I	II	I	II
High cardiac index						
15	8 10	6 45	1 0/120	150/110	688	766
17	7 75	5 40	198/130	190/122	836	1 200
18	4 97	6 70	220/150	210/140	1 382	920
20	5 82	4 65	148/78	141/80	590	730
Mean	6 66	5 81	184/120	173/113	887	904
Normal cardiac index						
20	3 83	5 00	146/90	128/80	1 179	798
24	3 75	3 17	132/87	126/84	1 344	1 526
26	3 61	2 97	155/110	168/114	1 350	1 734
31	4 72	5 06	144/94	136/86	1 000	856
10	3 59	3 77	138/90	122/82	1 326	1 131
12	2 75	3 04	134/85	136/82	1 450	1 315
13	4 00	4 10	185/105	186/97	1 635	1 553
15	4 49	5 13	170/105	165/105	1 242	1 071
Mean	3 83	4 03	151/96	146/91	1 316	1 248

Over 30 years of age

Table III Reproducibility of hemodynamic pattern admission to admission

Subject number	Dates of studies	Cardiac index		Blood pressure		Resistance		Remarks
		I	II	I	II	I	II	
2	Sept. 12, 1957							Not hypertensive on
	Nov 8, 1958	3 51	5 01	130/80	140/88	1 048	758	first admission
9	Oct 29 1957							Not hypertensive on
	April 4 1958	7 10	3 88	140 80	100/75	748	1 124	second admission
12.	March 28 1956							
	Dec. 3 1958	5 80	5 92	157/80	170/90	936	1 019	
14	Sept. 17 1958							
	May 8 1959	4 97	4 16	220/150	185/117	1 382	1 274	
6.	Jan. 28, 1960							
	Feb. 16, 1960	6 15	4 90	126/83	128/85	692	997	
3	May 1 1959							Not hypertensive on
	Dec 1 1959	5 04	3 42	180/100	140/92	1 000	1 205	second admission
4	Sept 1958							
	Sept., 1959	3 39	2 83	178 110	166/92	1 600	1 664	
9	Sept., 1957							
	April, 1961	3 06	2 86	120/80	128/88	1 251	1 470	

*Over 30 years of age

index were younger (34 as compared to 37) and possibly because of this had a somewhat shorter duration of known hypertension The family history of hypertension was less strong only 5 had a history of a parent with hypertension and none had had a parent who had died of hypertension. The parents alone were used in

the evaluation of the family history because only for them did our patients seem to have a satisfactory knowledge of the family medical history. The blood pressure and pulse of the subjects at the time of admission and the range of blood pressure while the subjects were in the hospital were similar for both groups under 50 whereas the complications were less common and less severe in those with a high cardiac index. Only the presence of a systolic murmur and an abnormal chest x-ray film which showed left ventricular enlargement were more frequent in those with an elevated cardiac output. For those over age 50 the groups appeared to be comparable in terms of complications.

Discussion

These data confirm the frequent occurrence of an elevated cardiac output and below normal total peripheral resistance in selected patients with an elevated blood pressure. In most subjects this pattern would appear to be consistent over 10 minutes, from day to day and if they

Table IV. Arterial and venous blood catecholamines in subjects with labile hypertension

Number	Cardiac index (L./min./M.²)	Total peripheral resistance (dynes cm.⁻⁵ sec.)	Catecholamines (mcg./L. plasma) Norepinephrine	Epinephrine
High cardiac index				
6	5.28	863	Arterial 16	37
			Venous 20	48
Normal cardiac index				
5	3.71	1,322	Arterial 43	40
			Venous 47	30
Mean for entire group	4.23 ± .92	1,160 ± 306	Arterial 34 ± 35	39 ± 55
			Venous 38 ± 40	37 ± 37
20 Normal subjects	3.61 ± .62	1,047 ± 180	Arterial 63 ± 55	42 ± 57
			Venous 64 ± 61	47 ± 63

Table V. Clinical characteristics of the two groups

	Number	Mean age	Complaint of hypertension on admission	Duration of hypertension known	Family history: Parent with hypertension	Family history: Parent died of hypertension	Systolic murmur	Eye grounds grade I	Eye grounds grade II	Abnormal urine (albumin)	X-ray*	ECG†
Under age 50												
High cardiac index	21	35	10	6.0	5	0	8	3	2	0	7	7
Normal cardiac index	31	39	10	7.2	14	7	4	8	5	4	6	11
Over age 50												
High cardiac index	6	55	2	9.5	1	0	1	4	2	1	5	4
Normal cardiac index	13	58	6	6.2	2	0	1	3	9	3	9	9

*Left ventricular enlargement.

†S-T, T-wave abnormalities and/or ventricular enlargement.

were hypertensive on both occasions from admission to admission. Thus it would appear that the hemodynamics may differ in subjects with labile hypertension and that these differences are not apparent when the measurement of blood pressure is used alone.

Why certain subjects should have an elevated output as a factor in their hypertension rather than the expected normal cardiac output and elevated total peripheral resistance is not clear. The hemodynamics are similar to those found in the anxiety state by Stead[4] and we might postulate that these were just anxious subjects who were frightened by the test procedure. If this is true, it would merely represent a different response to the standard stress of the test. However, although anxiety is difficult to evaluate, the subjects with an elevated cardiac index did not appear to be more anxious at the time of the test in terms of tachycardia, wide pulse pressure, sweating, or expressed anxiety; nor were they considered at the time of admission to the hospital to be more anxious than those with a normal cardiac output and elevated peripheral resistance. The measurement of oxygen consumption, which might help to assess anxiety, was not made. No other obvious explanation for the persisting high cardiac output could be found. Where measured, the protein bound iodine was similar for both groups. Using the Von Euler technique, which has the limitations of a low sensitivity, we could find no differences between the two groups in the levels of catecholamines in the blood. It is intriguing to speculate that the elevated cardiac output represents actually a new "set" in the cardiovascular regulating system, such as has been suggested by Gorlin to explain the syndrome of hyperhemorrhea.[9]

Although long-term follow-up is the only definitive answer to the usefulness of these hemodynamic measurements in the evaluation of the patient who presents with an elevated blood pressure, there is some evidence that the pattern of elevated output and low resistance may be milder or earlier. Wolf and Wolff[1] and Starr,[8] using the ballistocardiograph, have demonstrated that, when hypertensive, certain subjects with labile hypertension will manifest the high-output pattern, and these authors consider this to be a milder abnormality. Certainly, a lower than normal peripheral resistance is different from that usually seen in essential hypertension, as shown by several other workers.[4,6,11] Actually, the hemodynamics are similar to those seen in mild exercise,[12] which all agree is biological. Finally, there did appear to be differences in the clinical characteristics between the two hemodynamic patterns in those under 50 years of age, which suggests that the high-output pattern was milder. Only left ventricular enlargement, as observed by chest x-ray examination, was as common in the subjects with a low resistance, and this is said to be the least severe of the complications of hypertension.[3] It is of interest that these clinical differences were not present in the patients who were over 50 years old, which could be a function of the small number of observations, or it may be that over a certain age labile hypertension is a less significant abnormality.

There are, of course, certain obvious limitations to this kind of a study which should be emphasized. First, although many of the patients had been called hypertensive in the past, none actually had fixed essential hypertension. The possibility exists that none of the subjects in either group will go on to develop essential hypertension and hypertensive vascular disease, although this seems unlikely since labile hypertension is known to predispose to the development of fixed hypertension.[13] Second, the test situation is artificial and may have little to do with the day-to-day hemodynamics. Third, the separation into two groups is somewhat arbitrary, and considerable overlap must exist. Likewise, within each group some subjects barely had a single normal blood pressure recorded, whereas others fell promptly into the normal range and remained there during their stay in the hospital. These differences were not taken into consideration. Finally, even if the group with the elevated total peripheral resistance could be considered to have the more severe hypertension, the problem of whether the height of the resistance would correlate with the eventual severity of the hypertension has not been answered.

Summary

The hemodynamics have been studied in 73 subjects selected on the basis of an arbitrary definition for an elevated blood pressure Two hemodynamic patterns were observed (1) high output and low resistance, and (2) normal cardiac output and elevated total peripheral resistance. There is some theoretical and clinical evidence that the high cardiac output may indicate a more mild hypertension in terms of severity and the likelihood of the development of fixed essential hypertension. Final proof awaits long term follow up and such a study is underway

We wish to express our appreciation to Dr Robert B Chodos and Dr Nathaniel H. Bedalnes, of the Veterans Administration Hospital, Syracuse, N Y for their cooperation in making this study possible.

REFERENCES

1 Hamilton, M Pickering G. W Roberts, J A. F., and Sowry C S. C. A etiology of essential hypertension. 1 Arterial pressure in the general population, Clin. Sc. 13:11 1954.
2. Perera G. A. Hypertensive vascular disease; description and natural history J Chron. Dis. 1:33 1955
3 Cohen, G and Goldenberg, M The simultaneous fluorimetric determination of adrenalin and noradrenalin in plasma J Neurochem. 2:58 1957 58.
4. Frais E. D Hemodynamics of hypertension, Physiol. Rev 40:27 1960
5 Stead, E. A., Warren, J V., Merrill A. J and Brannon, E. S.: The cardiac output in male subjects as measured by the technique of right atrial catheterization Normal values with observations on the effect of anxiety and tilting, J Clin. Invest. 24:326 1945
6 Gorlin, R., Brachfeld N Turner J D Messer J V and Salazar E The idiopathic high cardiac output state, J Clin I vest. 38:2144 1959
7 Wolf S Cardon P V Shepard E M and Wolff H G Life stress and essential hypertension, Baltimore, 1955 Williams & Wilkins Co.
8 Starr I Ballistocardiographic studies of draftees rejected for neurocirculatory asthenia War Med 5 155 1944
9 Goldring W and Chasis, H Hypertension and hypertensive disease New York 1944 The Commonwealth Fund.
10 Bolomey A. A., Michie A. J Michie C Breed, E. S Schreiner G E and Lauson H D Simultaneous measurement of effective renal blood flow and cardiac output in resting normal subjects and patients with essential hypertension, J Clin. Invest. 28 10 1949
11 Varnauskas, E. Studies in hypertensive cardiovascular disease, Scandinav J Clin. & Lab Invest. 7: Suppl. 17 1955
12 Werko L., and Lagerlof H Studies on the circulation in man. IV Cardiac output and blood pressure in the right auricle, right ventricle and pulmonary arteries in patients with hypertensive cardiovascular disease, Acta med scandinav 133:427 1949
13 Donald, K. W Bishop, J M., Cummings, G., and Wade O L.: Effect of exercise on cardiac output and circulatory dynamics of normal subjects, Clin. Sc. 14:37 1955
14 Levy R. L Hillman, C. C Stroud W and White, P D Transient hypertension its significance in terms of later development of sustained hypertension and cardiovascular renal diseases, J.A.M.A 126:829 1944

Experimental and laboratory reports

Experimental studies on the pathogenesis of atrial arrhythmias in myocardial infarction

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In a clinicopathologic study of atrial arrhythmias beginning during acute myocardial infarction in man, a coronary occlusion was consistently found proximal to the origins of the arteries which supply both the sinus node and the A-V node and the sinus node was always infarcted.[1,2] Since it has been observed previously that simple ligation of the primary arterial supply of the sinus node in the dog is not associated with atrial arrhythmias,[3] this research was undertaken to study further the pathogenesis of these disturbances in rhythm during acute myocardial infarction. Primarily it is concerned with those factors which, in association with ischemia of the sinus node, might produce atrial fibrillation.

Method

Fifteen mongrel dogs were studied, and experiments were designed so that each animal served as its own control. Bipolar and unipolar electrocardiograms were recorded from the limbs with a direct-writing single-channel electrocardiograph. Atrial electrograms were not recorded in order to avoid the local stimulation of the atrial myocardium which a steel clip or other electrode would produce. Arterial and venous pressures were measured with mercury and saline manometers, respectively. Vagal stimulation was made with a Cambridge coil inductorium or a Grass stimulator, usually the former. When the cervical vagi were cut, the point of cutting was midway between the carotid sinus and the sternal notch. The experiments lasted from 3 to 6 hours in each dog.

Induction with ether was followed by administration of intravenous Nembutal (15 to 30 mg. per kilogram). The lightest plane of anesthesia in which the animal did not move about proved to be the most reliable for the purpose of this study. Intraperitoneal Nembutal or larger intravenous doses seemed to depress myocardial excitability.[4] Morphine alone and morphine plus succinylcholine were less satisfactory agents than Nembutal. After anesthesia, a standard right thoracotomy was used to expose the heart.

After control observations (Table I), the arteries which supply the region of the sinus node were ligated. With experience it became possible to do this with a minimum amount of trauma to the atrial myocardium. All of the arteries which were

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seen to approach the region of the sinus node were ligated but always at a distance from the node. Most ligatures were placed around the arteries in their course through epicardial fat or on the superior vena cava. From observations described later we are confident that the sinus node and its tracts of exit were never injured by the procedure of ligation which was the only time the atrium was touched. Since the ligatures usually did not include atrial myocardium and since they moved freely with the myocardium it is doubtful that they introduced any factor of local stimulation this was further supported by control procedures before and after the ligatures were placed

Results

A summary of the results is presented in Tables I and II As single procedures, neither ligation of the sinus node arteries stimulation of the vagus nerve intravenous injection of calcium nor intravenous injection of catecholamines was capable of producing an atrial arrhythmia in the

Table I Control procedures

Experiment	*Number of times performed*	*Number of dogs used*	*Number of times atrial arrhythmia† was produced*	*Number of dogs used*
Vagal stimulation only	39		0	–
Epinephrine or norepinephrine injection (intravenous) only	16	13	0	–
Calcium injection (intravenous) only	9	4	0	–
Calcium injection and vagal stimulation	6	1	3	1
Calcium and epinephrine or norepinephrine	1	1	1	1
Calcium and vagal stimulation and epinephrine or norepinephrine	4	1	2	1
Epinephrine or norepinephrine and vagal stimulation	7	1	3	1
Ligation of sinus node arteries only	15	15	0	–

*The same dogs

†"Atrial arrhythmia" here means fibrillation or flutter; it does not include sinus tachycardia after administration of epinephrine or norepinephrine, A-V nodal rhythm after vagal stimulation, or a few atrial premature beats

Table II Procedures after ligation of sinus node arteries

Experiment	*Number of times performed*	*Number of dogs used*	*Number of times atrial arrhythmia was produced*	*Number of dogs used*
Anemic anoxia (bleeding)	6	6	1	1
Anemic anoxia and vagal stimulation	4	2	0	–
Asphyxic anoxia	2		0	–
Chemical hypotension (trimethaphan)	3	2	0	–
Vagal stimulation	120	7	8	4
Calcium injection (intravenous)	12	6	0	–
Epinephrine or norepinephrine (intravenous)	47	14	8	2
Calcium and epinephrine or norepinephrine	2	1	0	–
Ligation of main coronary artery	9	6	0	
Vagal stimulation and epinephrine or norepinephrine	38	7	22	7
Calcium and vagal stimulation	18	6	3	3
Acetylcholine (intra-aortic)	7	4	1	1
Acetylcholine and epinephrine or norepinephrine	3	2	0	

*"Atrial arrhythmia" here means fibrillation or flutter; it does not include sinus tachycardia after administration of epinephrine or norepinephrine, A-V nodal rhythm after vagal stimulation, or a few atrial premature beats

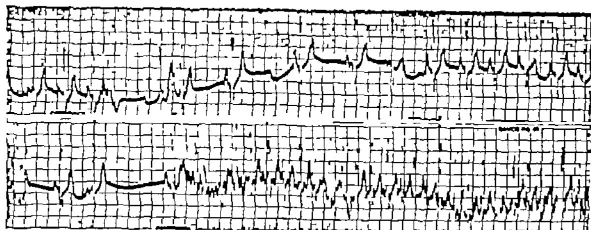


Fig. 1. The onset of atrial fibrillation during the removal of the fourth 100-c.c. increment of blood in a 30-minute period in one dog; the arteries to the sinus node had been ligated about 1 hour previously and the heart was not touched in the interim. There is periodic cessation of sinus node discharge shortly prior to the onset of the atrial fibrillation.

animals of this study. Combinations of procedures were variously successful in inducing atrial arrhythmias, both before and after ligation of the sinus node arteries, and the most successful combinations were ones which included stimulation of the vagus nerve. Details of the various experiments can be presented more clearly by combining a description of the procedure with the results obtained.

Ligation of the sinus node arteries. As in a previous study,[3] simple ligation of the major artery to the sinus node produced no significant disturbance in sinus rhythm. Because it has been shown that the collateral arterial circulation to the sinus node of the dog is extensive,[3] we attempted to ligate all of the visible arteries which approach the sulcus terminalis at the right auriculocaval junction. Many of these became visible only after ligation of the primary nodal supply. There are three principal routes of collateral circulation which may be provided by several arteries at each route: (1) down the superior vena cava, (2) up the medial wall of the right atrial appendage or through the anterior interatrial band (Bachmann's bundle), (3) lateral or anterolateral right atrial arteries, the primary artery to the canine sinus node being a posterior and terminal branch of the right coronary artery.[3,4]

Ligation of from 6 to 11 small arteries which supply the region of the sinus node sometimes produced visible pallor of that area, but normal sinus rhythm persisted in all of the animals except one, in which a few transient sinus pauses occurred for about 5 minutes after the ligations were completed. At some step in the experimental protocol the arteries to the sinus node were ligated in all 15 dogs. We concluded that compromise of all the visible arterial supply to the sinus node did not produce significant disturbance in sinus rhythm.

The sinus node was studied microscopically in 8 of the 15 hearts. Only one showed hemorrhage compatible with acute infarction, but which of the numerous experimental procedures performed was responsible is unknown. In 7 of the 8 the sinus node and surrounding atrial myocardium remained histologically normal even though all of its visible arterial supply had been ligated.

Compromise of the efficiency of collateral circulation. By making a large section of the entire circumference of the right atrium below the sinus node, including the adjacent interatrial septum, and examining this macroscopically and microscopically for arteries which were 0.5 mm. or more in diameter, we determined that there were no arteries of this size in the region of the sinus node which had not been ligated. The possibility remained that a significant amount of arterial blood was being supplied through very small arterial anastomoses. The major determinant of flow through

canine coronary arterial anastomoses has been shown to be perfusion pressure.[8] Consequently we elected to determine whether lowering the central aortic pressure after ligation of all the visible arterial supply to the sinus node produced atrial arrhythmias. This was considered to be particularly appropriate since it might be a factor which influences the onset of such arrhythmias in acute myocardial infarction in man in whom arterial hypotension is a common early feature.

The first method chosen for producing aortic hypotension was arterial bleeding. Arterial blood pressure was monitored with a catheter tip near the root of the aorta which reflected the pressure delivered to the coronary ostia. Femoral venous pressure was monitored at the same time. Arterial bleeding was carried out in 4 dogs in increments of 100 ml. over a period of 30 minutes. A total of 400 ml. was removed in 3 dogs and over 1,000 ml. in the fourth. In 2 other dogs 400 and 600 ml. were removed as quickly as flow would occur through a tube of 2 mm. internal diameter. In all 6 dogs the arteries to the sinus node had been ligated.

In 4 of the dogs which were bled no significant change in sinus rhythm occurred; the lowest pressures reached were 15 to 20 mm. Hg mean central aortic pressure. In the dog with a liter of blood removed atrial arrhythmias did not occur prior to the time at which we saw profound terminal disturbances in repolarization. In the sixth dog, which was bled gradually for 400 ml. atrial fibrillation began during the removal of the last 100-ml. increment of blood (Fig. 1); the sinus node arteries had been ligated 1 hour previously, but the region of the node and the remainder of the heart had not been touched subsequently. At the time of onset of atrial fibrillation the mean central aortic pressure was 34 mm. Hg (control pressure had been 140 mm. Hg) and the general function and gross appearance of the ventricular myocardium was good. Within a few minutes the blood which had been removed from this dog was reinfused and the pressure restored to control levels, but the fibrillation was unaffected. As might be expected, venous pressure in all 6 dogs gradually fell with bleeding.

To see whether a drop in central aortic perfusion pressure without associated anemic anoxia might disturb the function of the sinus node after ligation of the nodal arteries, transient hypotension was produced in 2 dogs with trimethaphan (Arfonad). Mean central aortic pressure was lowered from 150 to 30 mm. Hg. Normal sinus rhythm persisted. Trimethaphan produces general autonomic ganglionic blockade so that effects other than hypotension, e.g., vagal blockade, make the interpretation of results subject to certain questions which were not further evaluated.

We concluded that central aortic hypotension, which presumably reduces collateral arterial circulation to the sinus node after ligation of its visible arterial supply, is only occasionally (1 dog of 6) capable of disturbing the function of the sinus node as expressed by atrial arrhythmias. Thus hypotension may be a contributing factor in atrial arrhythmias during acute myocardial infarction but not a frequent nor dominant factor.

Acute anoxia. The effect of anoxia without initial hypotension or anemia was investigated in 2 thoracotomized dogs by disconnecting the respirator after the arteries to the sinus node had been ligated. We postulated that the sinus node, with its primary blood supply ligated, might show earlier or disproportionately severe evidence of ischemia. The expected results of progressive rise and then fall in central aortic pressure were observed; the aortic hypotension was associated with a marked elevation in venous pressure. Although marked hypoxia of the myocardium was obvious from its cyanosis as well as from electrocardiographic depression of the S-T segments, atrial arrhythmias did not occur.

Occlusion of the main coronary artery. Since the question under study was the onset of atrial arrhythmias during acute ventricular myocardial infarction, the effect of associated ventricular myocardial infarction was next examined. In 3 dogs the main right coronary artery, which supplies the sinus node artery, was ligated just distal to the conus artery; otherwise this would have been a potentially important route of collateral flow from the left anterior descending artery. This pro-

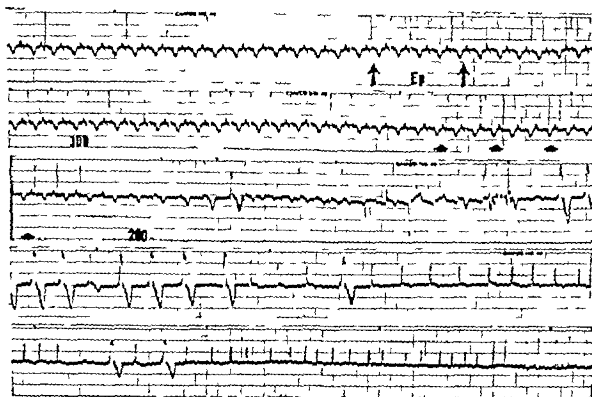


Fig. 24. Electrocardiogram of a dog which developed atrial arrhythmias during the peak pressor response to catecholamines (the sinus node arteries had been ligated). Epinephrine 0.1 ml. of 1:1,000 was injected between the arrows in the top strip; the other strips are a continuous recording. The small arrows in the second and third strips indicate increases of 20 mm. Hg in mean aortic pressure. At the peak pressor response in the third strip note that there is gradual bradycardia, disappearance of normal sinus pacemaking, and then the "spontaneous" onset of atrial fibrillation. After the initial few rapidly conducted beats the ventricular response is partially blocked (most of the fourth strip) but then gradually accelerates as the pressor effect of the epinephrine subsides.

duced acute cyanosis of most of the right ventricle but no disturbance in sinus rhythm; subsequent ligation of all visible collateral arteries to the sinus node still did not alter its rhythm.

In 3 other dogs the left circumflex ramus was ligated at its origin after all the visible arteries to the sinus node had been ligated. A lateral left ventricular infarction was obvious on direct inspection as well as electrocardiographically, but no disturbance in sinus rhythm occurred. In 2 of these 3 dogs the left anterior descending ramus was also ligated, and in the third dog the right coronary artery was also ligated; each ligation was made 30 minutes after the preceding one. This produced marked hypotension, obvious extensive ventricular infarction, and ventricular fibrillation 20 to 30 minutes later, but until that time sinus rhythm persisted.

Certain autonomic reflexes and other consequences of acute ventricular infarction may contribute to the onset of atrial arrhythmias, but in this small group they were not demonstrated to be an immediate effect. The results of the more prolonged evolutionary consequences of acute ventricular infarction may be more important but were not investigated. In particular the blood supply to the A-V node, which is complex in the dog,[7,9] may be an important contributing factor. Conditions associated with delayed A-V conduction observed in other experiments (asphyxic anoxia, terminally with anemic anoxia, and in one dog with multiple occlusions of the main coronary artery) presumably indicate impaired function of the A-V node, however, and were not associated with atrial arrhythmias.

Hypercalcemia. In man the blood level

of ionizable calcium has been reported to rise within hours after assumption of the supine position.[19] Although the extent of this rise is small its potential effect on the myocardium of a patient immobilized due to an acute myocardial infarction must be considered. To examine this factor cal cium chloride (100 mg. per milliliter) was slowly injected intravenously both before and after the arteries to the sinus node had been ligated in 6 dogs. The injection was at the rate of about 1 ml. per minute and the volume (average of 3 to 5 ml.) was the amount sufficient to produce Q-T shortening in the electrocardiogram. No changes occurred in cardiac rhythm. Other experiments with injection of calcium plus vagal stimulation are described under the latter heading.

Epinephrine and norepinephrine. After acute myocardial infarction epinephrine and other catecholamines appear in increased amounts in the blood.[22,23] Different doses of both epinephrine and norepinephrine were injected in 13 dogs, both before and after ligation of the arteries to the sinus node. Abrupt intravenous injection of less than 0.1 ml. of 1:1,000 epinephrine or norepinephrine produced moderate arterial hypertension and sinus tachycardia but no significant disorganization of the normal sinus rhythm whether the sinus node arteries had been ligated or not. In doses between 0.1 and 1.0 ml. the hypertension was more marked: it reached mean levels in the central aorta of 240 to 290 mm. Hg compared with control levels of 140 to 160 mm. Hg. At the point of most rapid rise in central aortic pressure the cardiac rhythm and conduction exhibited a reflex vagal effect which was the same for epinephrine or norepinephrine. In some animals this was sinus bradycardia, whereas in others there were varying degrees of A-V block, including transient complete A-V dissociation. All these effects could be blocked by prior administration of 0.5 mg. of atropine sulfate but they were not altered in the animals of this study by bilateral cervical vagotomy. In

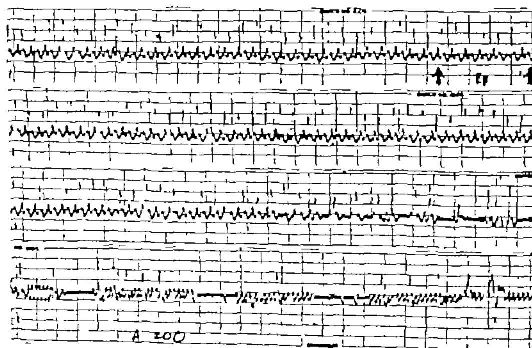


Fig. 2B. Electrocardiogram of a dog which developed atrial arrhythmias during the peak pressor response to catecholamines (the sinus node arteries had been ligated). The tracing, which is continuous, indicates the same response to an injection of epinephrine as that seen in Fig. 2A, with the onset of atrial flutter (with varying ventricular response) during the peak pressor response of 200 mm. Hg mean aortic pressure; this soon reverted to fibrillation before sinus rhythm resumed (not shown).

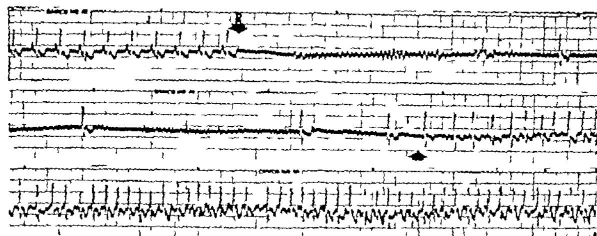


Fig. 3. An example of atrial fibrillation induced by vagal stimulation in a dog in which the sinus node arteries were ligated, and to which calcium had been administered (4 ml. of 10 per cent calcium chloride, slowly intravenously) just prior to the recording of this continuous electrocardiogram. Stimulation of the right vagus was begun at the arrow in the top strip and discontinued at the arrow in the second strip.

2 of the 13 dogs after ligation of the sinus node arteries (but not before) atrial fibrillation began during the peak of reflex vagal response to either epinephrine or norepinephrine (Figs. 2A and 2B) but there was no episode of fibrillation when atropine was administered.

We concluded that the cardiac accelerating effect of the catecholamines was insufficient alone to produce atrial arrhythmias in dogs with the arterial supply to the sinus node either intact or compromised but that a more marked pressor effect of these substances evoked a vagal reflex which sometimes produced atrial fibrillation in dogs in which the sinus node arteries were ligated. The same high level of pressor effect failed to produce atrial fibrillation when the arterial circulation to the sinus node was intact.

Other observations on the administration of catecholamines in conjunction with vagal stimulation are described in the section below.

Vagal stimulation. The effect of right vagal stimulation on the formation of sinus impulses increased from bradycardia to complete sinus arrest both with increasing voltage (and amperage) and with increasing frequency of the stimulus; the shape (sine or square) of the stimulating wave did not seem significant, nor did the duration of the impulse. The most effective frequency range was 20 to 40 cycles per second and the most effective voltage range was 3 to 5 volts. Higher frequencies and greater voltages were of no additional advantage, and were even detrimental in our attempt to induce atrial arrhythmias. Since both this frequency and voltage were possible with the coil inductorium and since it was simpler to use without extensive grounding to prevent distortion of the electrocardiogram, the coil inductorium was most often employed.

Seven dogs were utilized for studying the effects of vagal stimulation. After exposure of the two vagi in the neck, each nerve was stimulated separately and then the two simultaneously as control observations. Expected effects on the formation of sinus impulses and A-V conduction were always observed, but this stimulation alone did not produce atrial arrhythmias. Each stimulation was repeated at least twice and sustained for 10 to 30 seconds.

Both vagi were stimulated prior to cutting them in order to determine whether the central component of stimulation might alter its effect; it did not. In 5 dogs the left vagus was cut and the proximal end stimulated prior to cutting the right vagus; this produced an elevation of 10 to 30 mm. Hg in mean aortic pressure but no significant change in cardiac rhythm or A-V conduction. In one dog the proximal end of the cut right vagus was stimulated while the left was intact, again with no significant effect on cardiac rhythm or conduction.

Fig 4A Continuous electrocardiogram which demonstrates the development of atrial fibrillation from vagal stimulation *during the pressor response to epinephrine the sinus node arteries were ligated previously*. *This* combination (ligated sinus node arteries, administration of catecholamines, and vagal stimulation) most often produced atrial fibrillation. With a control mean aortic pressure of 130 mm Hg, 0.1 ml. of 1:1,000 epinephrine was injected intravenously between the arrows in the second strip. At the arrow with an *R* at the end of the third strip the right vagus nerve was stimulated the stimulus was discontinued at the arrow in the fourth strip when the mean aortic pressure was 230 mm Hg

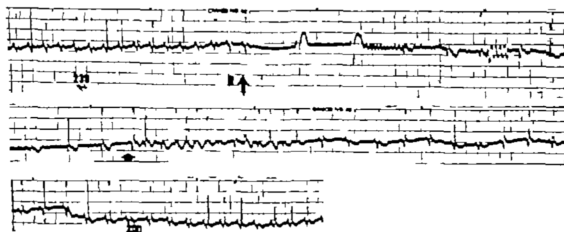


Fig 4B Continuous electrocardiogram which demonstrates the development of atrial fibrillation from vagal stimulation during the pressor response to epinephrine the sinus node arteries were ligated previously This combination (ligated sinus node arteries, administration of catecholamines, and vagal stimulation) most often produced atrial fibrillation. The right vagus was stimulated (arrow in the top strip) during the peak pressor response of 230 mm. Hg mean aortic pressure, and the stimulus was interrupted at the arrow in the second strip. On the resumption of sinus rhythm the mean aortic pressure was 200 mm. Hg

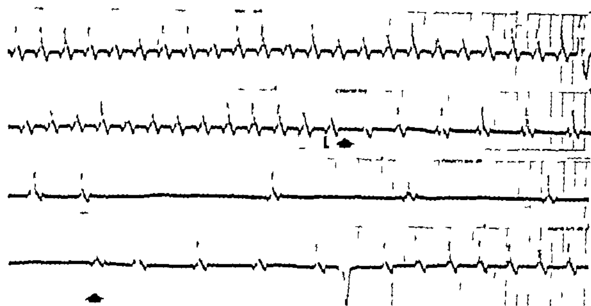


Fig. 5. A continuous electrocardiogram which demonstrates the disruption of an A-V nodal rhythm by stimulation of the left vagus applied at *L* in the second strip and discontinued at the arrow in the bottom strip. As the A-V node was suppressed, the ischemic sinus node (nutrient arteries ligated) resumed pacemaking for a few beats but then failed; the beats after this were infrequent A-V nodal escapes.

In 6 dogs, after control observations with vagal stimulation prior to ligation of the sinus node arteries, a slow intravenous infusion of 4 ml. of 10 per cent calcium chloride was given without producing any change in cardiac rhythm or conduction. Simultaneous vagal stimulation and injection of calcium while the heart was still untouched produced atrial fibrillation in one dog. In all 6 dogs the arteries which supply the sinus node were then ligated without disturbing cardiac rhythm. In all 6 the vagi were stimulated after the placement of sutures in the atrial epicardium but prior to ligation of the vessels in order to determine whether the creation of an irritable focus coupled with vagal stimulation would produce atrial arrhythmia; it did not on repeated tests. Additionally, after the arteries were ligated in these 6 dogs, vagal stimulation still rarely produced atrial arrhythmias. When calcium was administered to the same dogs after the sinus node arteries had been ligated and either the right or left vagus was stimulated, atrial fibrillation occurred 3 times in 18 attempts (Fig. 3). A number of the failures were technical errors due to unsatisfactory contact with the vagus nerve.

In 13 dogs in which the sinus node arteries were ligated, the effect of epinephrine or norepinephrine was studied (see above). We had observed that a reflex vagal response appeared during the maximal rise in central aortic pressure and that in 2 dogs atrial fibrillation followed this (Fig. 2). A preceding injection of calcium did not facilitate this type of production of fibrillation. In 7 dogs (sinus node arteries ligated), stimulation of either the right or left vagus nerve *during* the hypertensive response to either epinephrine or norepinephrine produced atrial arrhythmias (Figs. 4*A* and 4*B*) at least once in each dog. Since vagal stimulation alone in these same dogs had not produced atrial fibrillation before ligation of the sinus node arteries and only occasionally after, we concluded that the added effect of the catecholamines was significant. The cardiac accelerating effect plus the reflex vagal effect of the acute hypertension from catecholamines produced atrial fibrillation in only 2 of the 7 dogs, whereas the cardiac accelerating effect and the reflex vagal effect plus additional direct vagal stimulation produced atrial fibrillation in 7 of 7.

In one dog, right vagal stimulation after the administration of either calcium or epinephrine (the sinus node arteries were tied) occasionally failed to produce atrial

fibrillation when there was prompt assumption of regular pacemaking by an A V nodal focus. When this A V nodal rhythm was briefly sustained, the left vagus was stimulated because of its more prominent effect on the A V node and the A V nodal rhythm was thus terminated but atrial fibrillation did not occur (Fig 5)

To determine whether abrupt or sustained vagal stimulation had different effects in regard to the production of atrial arrhythmias one dog with the nodal arteries ligated was subjected to sustained right vagal stimulation with 5 volts at 10 c.p.s. and 10-msec. duration of the impulse this produced a reduction in sinus rate from 140 to 60 per minute. During this sustained bradycardia, 0 1 ml. of 1 1 000 epinephrine was given intravenously This produced the expected hypertension and slight additional slowing of the rate to 40 per minute, but no atrial fibrillation. During the peak hypertension a time at which abrupt vagal stimulation had been observed most often to produce atrial fibrillation under otherwise identical circumstances, the frequency of the sustained right vagal stimulation was increased in increments of 5 up to 40 c.p.s. This produced gradually increasing bradycardia but still no atrial fibrillation The limited observations from this one dog raise the question whether abrupt vagal stimulation is more likely to produce atrial fibrillation than is sustained or gradually increased stimulation

Another effect of the acute hypertension from catecholamines was a marked distention of the right atrium during the peak pressor response. Atrial distention is well known to predispose to atrial fibrillation it also produces reflex bradycardia which can be blocked with atropine.[13] To study atrial distention in one dog arterial blood was removed in increments of 100 ml. for a total of 400 ml over a period of 30 minutes. After each bleeding the response to vagal stimulation (the sinus node arteries were tied) was observed and no atrial arrhythmia was produced additionally at each step the observation was repeated after the intravenous in

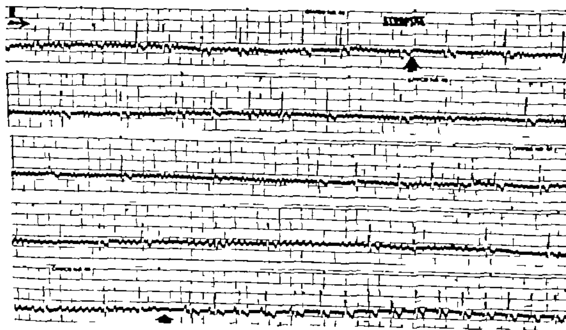


Fig 6 A continuous electrocardiogram during vagal stimulation which has produced atrial fibrillation in a dog in which the arteries to the sinus node were ligated 0.3 mg of atropine was injected intravenously at the second arrow in the top strip. Note that the fibrillation persists despite the vagal-blocking effect of the atropine Stimulation of the right vagus was stopped at the arrow in the fifth strip, at which time the fibrillation also terminated abruptly In similar experiments without atropine the fibrillation always persisted for a few seconds after vagal stimulation was discontinued.

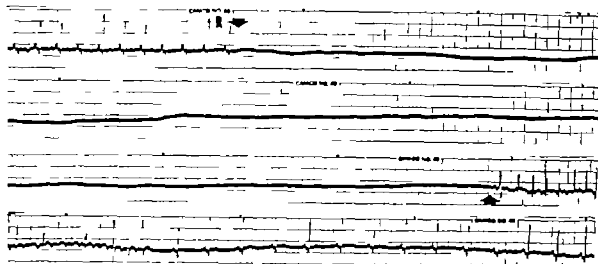


Fig. 7A. Continuous electrocardiogram which demonstrates the onset of atrial fibrillation just *after* the vagal stimulus was discontinued. The right vagus was stimulated at the arrow in the top strip and discontinued at the arrow near the end of the third strip; there is a brief period of atrial fibrillation and then a resumption of sinus rhythm.

jection of 0.1 ml. of 1:1,000 epinephrine but vagal stimulation still failed to produce atrial arrhythmia. This was in contrast to the usual success in producing atrial fibrillation with this combination of factors. At the end of this period of atrial deflation, the blood was replaced and then the injection of epinephrine and acute hypertension were again associated with marked atrial distention, whereas this had not been present during bleeding. Vagal stimulation was now capable of producing atrial fibrillation in 50 per cent of the attempts.

When atrial fibrillation began after vagal stimulation, whatever the associated experiment, the arrhythmia usually persisted for several seconds after the cessation of vagal stimulation. If the vagal stimulation was continued for up to 5 minutes the arrhythmia likewise persisted all this time plus several seconds after the stimulus was discontinued. In 2 dogs 0.5 mg. of atropine sulfate was injected intravenously during atrial fibrillation due to vagal stimulation with the stimulus continued; the fibrillation still persisted for as long as vagal stimulation was sustained (2 minutes) but a sinus rhythm abruptly appeared as soon as the vagal stimulation was discontinued (Fig. 6). Atrial fibrillation did not cease abruptly on cessation of vagal stimulation in any other experiments. That both dogs were given adequate amounts of atropine was indicated by an inability to evoke any effect on cardiac rhythm or conduction from stimulation of either the right or left vagus nerve immediately after the fibrillation stopped or for over 30 minutes after administration of the atropine. Whether the observations from these 2 dogs indicate delayed access of atropine to the ischemic sinus node and coincidental abrupt termination of atrial fibrillation at cessation of vagal stimulation (not otherwise observed in the current study) or whether they indicate the inability of atropine to terminate a vagally sustained atrial fibrillation so long as the vagal stimulus is continued, remains to be determined.

On several occasions a lingering vagal effect was observed in 3 dogs after cessation of vagal stimulation. With the sinus node arteries tied and the prior administration of either calcium or epinephrine, vagal stimulation failed to produce atrial fibrillation during the stimulation, but fibrillation began within a few heartbeats after the stimulus was discontinued (Figs. 7A and 7B). Other persisting vagal effects (A-V block, bradycardia) were also observed immediately after discontinuation of direct vagal stimulation in these dogs. This lingering vagal effect may have been due to the atrial distention which occurred during prolonged vagal stimulation and asystole and which was relieved only sev-

eral beats *after* sinus rhythm returned. That fibrillation began after atrial motion resumed and not during the period of stronger vagal effect may indicate that motion of the atrial myocardium is itself a contributing factor.

Although atrial fibrillation could be produced by stimulation of either the right or left vagus nerve—with other conditions appropriate—it was slightly easier to produce the arrhythmia with stimulation of the right vagus nerve. Once the atrial fibrillation was produced, however, it could be sustained indefinitely by quickly shifting from stimulation of one vagus nerve to the other.

Vagal stimulation during asphyxic anoxia, anemic anoxia, or occlusion of the main coronary artery (the sinus node arteries were tied) did not produce atrial fibrillation unless there was prior administration of calcium or catecholamines, or unless the atrium was markedly distended. Catecholamines were the most effective of these potentiating factors.

Acetylcholine was injected slowly into the root of the aorta on several occasions in 3 dogs in which the sinus node arteries were ligated. The effect was monitored electrocardiographically and the injection stopped when either an intense bradycardia or A-V block occurred; the amount of acetylcholine required for this effect averaged about 100 mg. Complete A-V block regularly occurred before there was any discernible effect on the impulse rate of the sinus node; additional injection slowed the sinus node ultimately to a standstill, but atrial fibrillation occurred on only one occasion in 7 experiments. The prior administration of epinephrine or calcium did not facilitate an arrhythmic response to acetylcholine. Since the supply of blood to the sinus node was cut off by ligation, a delayed access of acetylcholine to the node may have influenced these results. The injection of larger doses and topical application of acetylcholine were not studied.

Discussion

Atrial arrhythmias which begin after sudden compromise of the blood supply to the sinus node are due to complex factors and not simply to production of nodal ischemia. Every cardiac physiologist has observed intensely hypoxic hearts which maintain a normal sinus rhythm, and that an excised segment of atrial muscle including the sinus node will also continue to beat regularly. It must be noted, however, that these latter states involve homogeneous hypoxia, and observations from them cannot necessarily be applied to the behavior of the sinus node which is selectively made hypoxic while other parts of the atrium continue to be oxygenated normally. That focal ischemia of the sinus

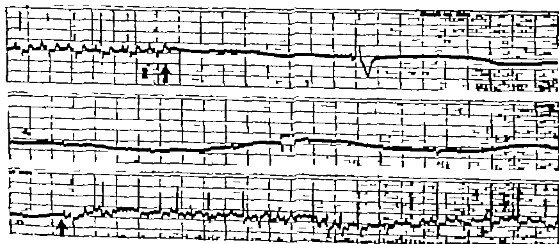


Fig. 7B. Continuous electrocardiogram which demonstrates the onset of atrial fibrillation just *after* the vagal stimulus was discontinued. Stimulation of the right vagus at the arrow in the first strip is followed by a few sinus escape beats but no fibrillation until the vagal stimulus was discontinued at the arrow in the last strip.

node may contribute to the onset of atrial fibrillation is suggested by the fact that this arrhythmia can occasionally be produced by stimulation of the vagus nerve or injection of a catecholamine after ligation of the sinus node arteries, whereas neither of these procedures produced atrial fibrillation if arterial circulation to the node was intact.

In the presence of nodal hypoxia induced by ligation of all visible supplying arteries, this study indicates that at least two other factors are still usually necessary in order to produce atrial fibrillation *frequently*. One of these factors is vagal stimulation and the other may be either atrial distention or the administration of calcium or catecholamines. Others have previously pointed out that atrial fibrillation could be produced experimentally by the interaction of two factors on the atrial myocardium and that a common denominator in these experiments was that one of these factors was vagal stimulation.[11, 4] Nahum and Hoff[7] studied the effects of thyroxin and electrical stimulation as the nonvagal factors and included these among other nonvagal agents which they named "E factors." On the basis of both the present study and those of Winterberg,[10, 4] the catecholamines and calcium should also be considered "E factors." Ischemia of the sinus node may be another "E factor" but when of brief duration (a few hours) it does not appear to be so potent as the others mentioned.

It is important to understand how all these factors in the production of experimental atrial fibrillation interact. The administration of epinephrine, for example, not only has a positive chronotropic effect but it also has a reflex vagal effect; furthermore, during the peak hypertension the right atrium distends, which favors the onset of fibrillation and also may compound the reflex vagal effect from stretch receptors in the aorta and large arteries.[21] Calcium not only shortens the atrial refractory period in a manner similar to the action of acetylcholine, but it also produces other vagomimetic effects.[17, 18] The common factor in most of these variables is a vagomimetic influence. Thus their contribution to the pathogenesis of atrial fibrillation in these experiments may be only through their facilitation of the effect of vagal stimulation. Since maximal vagal stimulation (to the point of cessation of sinus nodal activity) failed to produce atrial fibrillation when employed alone, the explanation is probably not so simple.

Whether atrial fibrillation can be induced by vagal stimulation alone is controversial, although the weight of evidence suggests that it rarely can. In a careful analysis of this question, Iglauer, Davis, and Altschule[19] concluded that the induction of atrial fibrillation by vagal stimulation alone occurs exceedingly infrequently. Lewis, Drury, and Bulger[20] made the same statement. The principal objection to experiments which claim to produce atrial fibrillation in this manner has been the employment of an electrode attached to one of the atria, which acts as a local direct stimulus.[19] Whether the production of atrial fibrillation by acetylcholine or similar substances can be interpreted as a simulated vagal effect is uncertain. Although the amounts of acetylcholine administered are far above the amounts conceivably produced in vivo after vagal stimulation,[19] the concentrations reached at effector sites may well be less.

There is also controversy whether atrial fibrillation can be produced by the administration of supraphysiologic amounts of vagomimetic substances; some investigators claim consistent success,[11, 20, 22] whereas others deny that this can occur at all.[11] In addition to local irritant factors (electrode for atrial electrograms, for example), one reason for such discrepancies is the effect of certain barbiturates on the facility of experimental production of atrial fibrillation. It has been repeatedly demonstrated that barbiturates significantly depress the likelihood of producing experimental atrial fibrillation,[4, 11] and one of the more successful studies on the production of atrial fibrillation with vagomimetic substances made a point of using unanesthetized animals for this reason.[19] In the present study, light anesthesia with intravenous Nembutal was employed and heavier doses of this drug seemed to lessen the chance of production of atrial fibrillation. Since the same drug in the same amount was present during both the control and subsequent procedures, however,

it does not alter the conclusions based on comparisons of various procedures before and after ligation of the sinus node arteries.

Suppression of normal activity in the sinus node from which the spread of atrial excitation is normally accomplished should predispose to the occurrence of a disorganized rhythm. That this actually is true is indicated by the studies of Loomis and Krop[33] who found that crushing the sinus node or slowing it by the local application of ice facilitated the experimental production of atrial fibrillation. Activity of the sinus node is suppressed by vagal stimulation, but in the present study another contributing factor to such suppression was focal ischemia of the node.

In addition to suppression of the sinus node (especially by the right vagus) and slowing of A-V conduction (especially by the left vagus) stimulation of the vagus nerve increases the normal disparity of repolarization speed in atrial fibers and thus favors the onset of fibrillation.[31,32] The normal disparity of repolarization speed in atrial fibers may be increased by substances which either delay or accelerate repolarization. Thus, although stimulation of the vagus nerve suppresses the rate of sinus node discharge, and the administration of epinephrine accelerates it, both of these may increase the normal disparity of repolarization speed in the atrial fibers. It may be the repolarization effect on atrial fibers by both calcium and catecholamines which accounts for their potentiation of an arrhythmic response to vagal stimulation.

Although the experiments were designed to approach as closely as possible the production of "spontaneous" atrial fibrillation without faradic or aconitine stimulation of atrial muscle directly (also the reason an electrode was not attached to the heart) the unavoidable small amount of trauma associated with ligation of tiny atrial arteries introduced a minor local irritant factor. That this was probably not significant is indicated by the absence of atrial fibrillation from vagal stimulation after placement of multiple untied sutures in the atrial epicardium.

Applicability of the results of this study to the pathogenesis of atrial arrhythmias during myocardial infarction in man is limited because of the difference in coronary anatomy of the dog and man. For example, an occlusion of the right coronary artery in man can be proximal to the origin of the nutrient arteries to both the sinus and the A-V nodes in about 55 per cent of the patients.[9,34] In the dog there is no means of compromising the supply of blood to both nodes by a single coronary occlusion, for the sinus node is virtually always supplied by the right coronary artery which furnishes almost none of the supply of blood to the A-V node. Furthermore a separate series of ligations to compromise the supply of blood to the canine A-V node is complicated by the multiple sources of major supply to that node from the terminal portion of the left circumflex artery and from the diagonal canine septal artery.[8] Thus, the experimental production of ischemia of both the sinus and the A-V nodes simultaneously in the dog introduces more extraneous variables than are desirable.

An intact A-V node may diminish the likelihood of producing experimental atrial fibrillation because it is an efficient alternate pacemaker. In a clinicopathologic study of atrial arrhythmias which occur during myocardial infarction in man, the occlusions of the main coronary artery were proximal to arteries supplying both the sinus node and the A-V node in every case.[15] Several times in this study the suppression of the activity of the sinus node by stimulation of the right vagus nerve failed to produce atrial fibrillation (other conditions being appropriate) when there was prompt onset of A-V nodal rhythm.

Our inability to render the A-V node ischemic without introducing unwanted other variables was partially overcome by vagal suppression of this node. Even though the left vagus nerve usually has a more profound effect on the A-V node, this selectivity varies considerably in different dogs, and there is virtually always some cross-influence of the right vagus nerve on the A-V node and of the left vagus nerve on the sinus node. Additionally, the reflex vagal responses to acute hypertension and atrial distention, as well as the vagomimetic effect of calcium, may be expected to influence the sinus node and the A-V node equally.

Infarction of the sinus node which was

observed in all of the hearts from patients with onset of atrial arrhythmias during acute myocardial infarction[1,2] was present in only 1 of 8 canine hearts examined microscopically. Since the maximal duration of these experiments in dogs was a few hours, whereas the patients survived for many days, the difference in nodal histology was most likely due to the difference in duration of nodal ischemia. This is additional evidence which suggests that chronic or prolonged ischemia of the sinus node may have a different effect on cardiac rhythm than that observed during the relatively brief ischemia in the present study.

Summary

To determine the pathogenesis of atrial arrhythmias which begin during acute myocardial infarction a series of experiments based on focal ischemia of the sinus node were performed in 15 dogs. Rendering the sinus node ischemic by ligation of all of its visible supply of blood did not produce atrial fibrillation. Lowering the coronary perfusion pressure and presumably impairing collateral arterial flow after ligation of the sinus node arteries produced atrial fibrillation in 1 of 9 experiments.

Vagal stimulation did not produce atrial fibrillation as a control procedure but occasionally produced atrial fibrillation in dogs in which the arteries to the sinus node were ligated. Administration of calcium to the same dogs did not produce atrial fibrillation, until the vagus nerve was also stimulated. Intravenous injection of epinephrine or norepinephrine sometimes produced atrial fibrillation after the sinus node arteries were ligated (but not before) and this could be prevented with atropine. Vagal stimulation after administration of either calcium or catecholamines to dogs in which the sinus node arteries were ligated most consistently produced atrial fibrillation.

Most of these variables had interacting effects. One possible common effect of all the variables was an increase in the normal disparity of repolarization speed in atrial fibers, which is known to facilitate the onset of atrial fibrillation. Of contributory importance was the suppression of the formation of sinus impulses by vagal stimulation and the probable weakening of the formation of these impulses by nodal ischemia.

REFERENCES

1. James, T. N.: Myocardial infarction and atrial arrhythmias: clinical, pathologic, and experimental studies, Circulation 22:767, 1960.
2. James, T. N.: Myocardial infarction and atrial arrhythmias, Circulation 24:761, 1961.
3. James, T. N., and Reemtsma, K.: The response of sinus node function to ligation of the sinus node artery, Henry Ford Hosp. Med. Bull. 8:129, 1960.
4. Van Dellen, T. R., Roberts, R. C., and Miller, J. R.: The effect of pentobarbital on cardiac conduction system of the digitalized dog's heart, Am. Heart J. 23:772, 1942.
5. Halpern, M. H.: Arterial supply to the nodal tissue in the dog heart, Circulation 9:547, 1954.
6. Kattus, A. A., and Gregg, D. E.: Some determinants of coronary collateral blood flow in the open-chest dog, Circulation Res. 7:628, 1959.
7. Halpern, M. H.: Blood supply to the atrioventricular system of the dog, Anat. Rec. 121:733, 1955.
8. Lumb, G., Shacklett, R. S., and Dawkins, W. A.: The cardiac conduction tissue and its blood supply in the dog, Am. J. Path. 35:467, 1959.
9. James, T. N.: Anatomy of the coronary arteries, New York, 1961, Paul B. Hoeber, Inc.
10. Kleitman, N.: Sleep and wakefulness, Chicago, 1939, University of Chicago Press.
11. Richardson, J. A., Woods, E. F., Gates, P. C., and Bagwell, E. E.: Plasma catecholamines in coronary occlusion and angina pectoris, Fed. Proc. 18:437, 1959.
12. Richardson, J. A., Woods, E. F., and Bagwell, E. E.: Circulating epinephrine and norepinephrine in coronary occlusion, Am. J. Cardiol. 5:613, 1960.
13. Aviado, D. M., Jr., and Schmidt, C. F.: Reflexes from stretch receptors in blood vessels, heart and lungs, Physiol. Rev. 35:247, 1955.
14. Nahum, L. H., and Hoff, H. E.: Auricular fibrillation in hyperthyroid patients produced by acetyl-β-methylcholine chloride, with observations on role of vagus and some exciting agents in the genesis of auricular fibrillation, J. A. M. A. 105:254, 1935.
15. Winterberg, H.: Studien über Herzflimmern. II. Mitteilung. Über die Bedeutung des Herzflimmerns durch einige Gifte, Arch. ges. Physiol. 122:361, 1908.
16. Winterberg, H.: Studien über Herzflimmern. I. Mitteilung. Über die Wirkung des Nervus Vagus und accelerans auf das Flimmern des Herzens, Arch. ges. Physiol. 117:223, 1907.
17. Goodman, L. S., and Gilman, A.: Pharmacological basis of therapeutics, ed. 2, New York, 1958, The Macmillan Company.
18. Hoffman, B. F., and Cranefield, P. R.: Electrophysiology of the heart, New York, 1960, McGraw-Hill Book Company, Inc.

19 Iglauer A., Davis, D and Altschule, M.D Auricular fibrillation in normal, intact animals after the intravenous injection of Mecholyl (acetyl-β-methylcholine) AM. HEART J 22:47 1941.

20. Lewis, T Drury A. N and Bulger H A: Observations upon flutter and fibrillation. Part VII The effects of vagal stimulation Heart 8:141 1921

21 Scherf D and Chick, B Abnormal cardiac rhythms caused by acetylcholine, Circulation 3:764, 1951.

22. Burn, J H Williams, E.M V and Walker J M The production of block and auricular fibrillation in the heart-lung preparation by inhibitors of cholinesterase, Brit. Heart J 17:431 1955.

23. Loomis, T A., and Krop, S. Auricular fibrillation induced and maintained in animals by acetylcholine or vagal stimulation, Circulation Res. 3:390, 1955

24. Alessi R Nusynowitz, M. Abildskov J A and Moe, G K. Nonuniform distribution of vagal effects on the atrial refractory period Am. J Physiol 194:406 1958.

25 Moe G K., and Abildskov J A. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge, AM. HEART J 58:59 1959

26 James, T N and Burch G E The atrial coronary arteries in man, Circulation 17:90, 1958.

Hemodynamic and metabolic effects of angiotensin II during rest and exercise in normal healthy subjects

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Angiotensin II is a synthetic thermostable octapeptide which causes contraction of the smooth muscle of systemic blood vessels and other tissues. When injected intravenously it causes a prompt short-lived pressor response which is not inhibited by ganglionic blockade or subject to tachyphylaxis. It exerts no known direct cardiac inotropic or chronotropic effects, although reflex bradycardia results from the systemic pressor response. The action of renin upon renin substrate is believed to produce the decapeptide angiotensin I. A converting enzyme in plasma splits off the terminal 2 amino acids, histidine and leucine, to produce the active vasoconstrictor angiotensin II. The latter is degraded to amino acids by angiotensinase, an enzyme present in normal kidney, erythrocytes, and various tissues.[1,2]

Since direct techniques of identification have not yet demonstrated either renin or angiotensin in human blood, Peart[3] doubts their importance in human physiology and hypertension. Nevertheless, hemodynamic effects of angiotensin II have been studied in human subjects (Table I). When blood pressure is raised to hypertensive levels, it reduces effective renal plasma flow and urinary output and produces a slight retention of sodium in normotensive patients.[4] These effects persist as long as hypertension is maintained. Hypotensive patients infused with angiotensin II have shown an increase in the output of urine, which is presumably due to more adequate perfusion of the kidneys. Finnerty and associates found no change in blood volume during experiments on normotensive patients and pressor-equivalent doses of l-epinephrine blocked vasoconstrictive effects of angiotensin II. Segel and associates[5] found evidence of pulmonary as well as systemic vasoconstriction, whereas others believed there was no direct effect on pulmonary arteries or veins.[6,7]

Methods

Ten normal healthy male volunteers were studied while they were in the fasting state without sedation. Cardiac output was measured by the direct Fick principle utilizing cardiac catheterization for sampling of mixed venous blood from the right atrium or pulmonary artery. Pressures were recorded with a Statham P 23D pressure transducer. Arterial pressures and samples were obtained by means of a No. 18 Cournand needle inserted into a peripheral artery. Oxygen consumption and ventilation were measured with a 13-liter Collins spirometer. Indicator-dilution curves were recorded in some instances by means of an ear oximeter, using Evans blue dye

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Augmented central blood volume[*] was calculated from mean circulation time and cardiac output derived by the Fick principle. The peripheral resistance index (PRI) was calculated by means of the formula

$$PRI = \frac{\text{Arterial Mean Pressure} \times 80}{\text{Cardiac Index}}$$

which yields resistance units in dynes seconds centimeters^{-5} times square meters of body surface area (dsc.$^{-5}$ $\times$ M^{2}). Apparent work of the left ventricle was calculated from the formula

$$\text{Work (Kg M./min.)} = \frac{MAP \times CO \times 14.5}{1\,000}$$

where MAP is mean arterial pressure, CO is cardiac output, and 14.5 is a constant derived from the product of the specific gravities of blood and mercury. Coronary blood flow was measured by the nitrous-oxide desaturation technique[9] after catheterization of the coronary sinus in 3 individuals. The temperature of the skin was recorded with a Rauh thermocouple.

Lactic acid was determined by the method of Barker and Summerson,[10] pyruvic acid by the method of Segal and co-workers,[11] free fatty acid (FFA) by the modified Dole procedure,[12] and glucose by the method of Beach and Turner[1] modified by Halsey.[14] Excess lactate (XL) for appraisal of anaerobic metabolism during experimental periods was calculated from Huckabee's formula[15]

$$XL = (L_n - L_o) - (P_n - P_o)(L_o/P_o)$$

where L_o and P_o represented concentrations of lactic acid and pyruvic acid in arterial blood during control periods and L_n and P_n represented concentrations during experimental periods.

Procedure

Control measurements were made when the subjects were in the resting steady state condition while lying supine; then angiotensin II* was infused intravenously either into the right heart or into the pulmonary artery. The dosage was .05 micrograms per kilogram per minute (averaging 3 to 4 micrograms per subject per minute) for 30 to 60 minutes. Sufficient time was allowed for the blood pressure and heart rate to stabilize before measurements were made. Three subjects were also studied while they did leg exercises in the supine position with and without angiotensin II. Another subject was studied while he

*Mean circulation time which is measured by arterial sampling is shorter than that which is measured by capillary sampling by the earpiece oximeter. Therefore, central volume will be greater (augmented) with the latter method.

*Lyophilized crystals of Valyl[5] angiotensin II for this study were supplied by Ciba Pharmaceutical Products, Inc.

*Table I. Hemodynamic effects of synthetic angiotensin reported by others in patients without cardiovascular diseases**

	Control	*Angiotensin*	*Number of observations*	*Per cent change‡*
Mean arterial pressure (mm. Hg)	91	123	42	+35
Mean pulmonary arterial pressure (mm. Hg)	14	20	20	+43
Peripheral resistance (dsc.$^{-5}$)	1,220	1,780	23	+57
	(2,122)†	(3,530)†	(26)†	
Cardiac output (L./min.)	6.2	5.5	23	−14
	(3.5)	(2.9)	(26)	
Stroke volume (ml.)	78	79	23	+2
	(44)	(43)	(26)	
Heart rate	80	67	31	−16
Oxygen consumption (ml./min.)	237	240	15	+1
	(134)	(136)		
Left ventricular work (Kg. M./min.)	8.8	10.3	23	+13.5
	(4.8)	(5.3)	(26)	
Arteriovenous oxygen difference (ml./L.)	39.6	45.9	15	+16

*Combined and averaged data of Lichtlen, et al.[3] on 5 subjects, of Bancetta, et al. on 8 subjects, of Finnerty, et al. in 22 studies on 17 subjects, and of Segal, et al. in 10 studies on 7 subjects.
†Parenthesized data have been corrected for body surface area.
‡For all available data.

Table II. Hemodynamic and metabolic effects of angiotensin II in fasting supine normal subjects at rest

	Number of observations	Control	Angiotensin II	Per cent change	Significance of change ("p" value)
Mean arterial pressure (mm. Hg)	10	97.5 ± 9.5	127.7 ± 10.2	+31	< .001
Peripheral resistance index (dsc. M.²)	10	1,866 ± 501	3,149 ± 710	+68.8	< .001
Arteriovenous oxygen difference (ml./L.)	10	45.4 ± 8.0	56.9 ± 9.9	+25.3	< .01
Cardiac index (L./min./M.²)	10	4.46 ± 1.13	3.42 ± .57	−23.5	< .02
Stroke index (ml./M.²)	10	65.3 ± 14.5	51.8 ± 9.6	−20.7	< .05
Oxygen consumption (ml./min./M.²)	10	196 ± 45	188 ± 34	−4.1	> .1
Heart rate	10	69 ± 12	68 ± 16	—	> .1
Left ventricular work (Kg.M./min./M.²)	10	6.3 ± 1.6	6.3 ± 1.2	—	> .1
Free fatty acids (µEq/L.)	9	854 ± 325	717 ± 276	−16.0	> .1
Glucose (mg. %)	9	79.2 ± 6	84.9 ± 13.9	+7.1	> .1
Lactic acid (mM./L. of blood H_2O)	9	0.633 ± 0.218	0.717 ± 0.213	+13.3	> .1
Pyruvic acid (mM./L. of blood H_2O)	9	0.036 ± 0.017	0.034 ± 0.009	—	> .1
"XL" (mM./L. of blood H_2O)	9	0.000	0.011	—	—

*Mean ± standard deviations.
Mean body surface area = 1.93 M.²

walked on the motor-driven treadmill during an infusion of angiotensin II. Coronary sinus catheterization was performed in 3 other subjects.

Results

Hemodynamic and metabolic data obtained from 10 subjects before and during infusion of angiotensin II are presented in Table II.

I. General circulatory effects. A significant increase in both systolic and diastolic blood pressure occurred within 1 minute. Mean arterial blood pressure increased by 31 per cent, from an average of 98 to 128 mm. Hg. The average systemic resistance rose 69

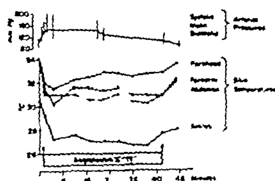


Fig. 3. Responses of temperature of skin and blood pressure to angiotensin II in a representative subject.

per cent, from 1,866 to 3,149 dsc.⁻⁵M.² Cardiac index (C.I.) fell from an average of 4.46 to 3.42 L./min./M.² Since heart rate did not change, this fall was due to a corresponding decrease in stroke index (SI) from an average of 65 to 52 ml./M.² Angiotensin II caused no significant change in augmented central blood volume in 3 instances. In spite of the significant increases in arterial pressure and peripheral resistance, the average calculated apparent work of the left ventricle per minute did not change, because of the compensatory fall in cardiac output.

II. Pulmonary circulation. Pulmonary arterial pressure was monitored in 4 subjects and increased from an average mean pressure of 11 to 17 mm. Hg. Right atrial pressure rose in 3 subjects, from 4 to 6.5 mm. Hg on the average. Neither of these pressures rose at the same time that the systemic arterial pressure did, but required several minutes to increase gradually, even though the angiotensin II reached the pulmonary artery and right atrium before the peripheral arteries. Thus, in this dosage angiotensin II had no immediate effect upon the pulmonary vasculature, which finding confirms the data of Eckert and Rose[7] who infused angiotensin II into the isolated pulmonary circuit of

dogs and observed no rise in pressure Maxwell and associates[8] also found no rise in pulmonary arterial pressure in intact dogs.

III Cutaneous circulation Serial measurements were made of the temperature of the skin of the forehead forearm abdomen and ankles, in order to assess regional differences in vasoconstrictor responses to angiotensin II Fig 1 illustrates these observations in a representative individual The temperature of the skin of all areas studied dropped within 3 minutes as blood pressure rose. The greatest decline occurred in the distal parts of the lower extremities. Within 5 minutes after the infusion was discontinued the temperatures in all areas increased toward initial control levels, concomitant with a fall in blood pressure.

In the course of these studies, angiotensin II (1μg/c.c.) was inadvertently infiltrated subcutaneously in two individuals. In one the infiltration was not detected for several minutes. No pressor rise was seen in either individual as a result of this infiltration. There was no local reaction of tissue at that time or subsequently

IV Systemic metabolic effects Oxygen consumption did not change in response to angiotensin II but there was a significant compensatory increase in arteriovenous oxygen difference from 45 4 to 56.9 ml /L. of blood flow The level of free fatty acid in arterial blood was not significantly altered by the infusion of angiotensin II although it tended to fall slightly from 854 to 717 microequivalents per liter Lactic acid pyruvic acid and glucose did not change significantly XL ranged from −.59 to +.32 (average + 01) millimoles per liter of blood water Since this represented less than 1 per cent of total body oxygen consumption the increased arteriovenous oxygen difference observed during infusion of angiotensin II fully compensated for any impairment of oxygen transport caused by decreased cardiac output

V Myocardial metabolism Effects of angiotensin II on coronary blood flow and myocardial oxygen consumption in 3 subjects are shown in Table III Coronary blood flow myocardial arteriovenous oxygen difference and myocardial oxygen consumption changed very little, whereas arterial pressure increased 25 per cent and systemic arteriovenous oxygen difference increased 37 per cent This was consistent with the lack of change in apparent work of the left ventricle.

VI Responses with exercise Table IV summarizes the hemodynamic data in 3 subjects during supine leg exercise before and during the infusion of angiotensin II

Table III *Myocardial observations in 3 individuals (average values)*

	Control	*Angiotensin*
Cardiac output (L./min)	9 23 (5 1)*	7 06 (3 9)*
Stroke volume (ml.)	140 (77 4)	110 (61 4)
Arteriovenous oxygen difference (ml./L.)	37 0	50 6
Arterial pressure (mm. Hg)	103	129
Peripheral resistance (dsc.⁻⁵)	930 (1 682)	1 463 (2 650)
Left ventricular work (Kg M./min.)	13 5 (7 5)	13 2 (7 3)
Coronary blood flow (ml /min./100 Gm.)	85	90
Myocardial arteriovenous oxygen difference (ml./L.)	129 1	124 4
Myocardial oxygen consumption (c.c./min./100 Gm)	11 0	11 2
Body surface area	1 81	

*Parenthetical data have been corrected for body surface area.

Table IV *Effects of angiotensin II on exercise hemodynamics in 3 normal subjects (average values)*

	Control exercise	*Exercise + angiotensin II*
Mean arterial pressure (mm Hg)	111	121
Peripheral resistance index (dsc.⁻⁵ M.)	1 335	1 610
Arteriovenous oxygen difference (ml /L.)	83 2	87 3
Cardiac index (L./min./M)	6 1	5 9
Stroke index (ml.)	64	65
Oxygen consumption (ml /min /M)	520	534
Heart rate	93	91
Left ventricular work (Kg M /min./M)	9 9	10 2

Body surface area = 91

Mean arterial pressure rose from an average of 111 to 121 mm. Hg. The mean PRI increased from 1,355 to 1,610 dsc $^{-4}$M^{2} and CI fell slightly from 6.1 to 5.9 L./min./M.^{2} SI did not change, and heart rate decreased slightly from 95 to 91. Oxygen consumption did not change significantly, but arteriovenous oxygen difference again showed a slight compensatory increase from 83.2 to 87.3 ml./L. of blood flow. Apparent left ventricular work per minute did not change significantly because of the slight decrease in CI. Since pressure and PRI did not rise as high with angiotensin during exercise as during rest (1,610 as compared to 3,149 dsc $^{-4}$M^{2}), the normal vasodilatory response to exercise in skeletal muscle still occurred. Under these circumstances vasoconstriction must be largely limited to the visceral organs and nonexercising muscles.

VII. Effect on orthostatic hypotension. Orthostatic hypotension has been reported as a sequel to infusion of angiotensin II in normotensive patients.[4] This occurred in one of our subjects several minutes after the infusion was stopped while he was supine. When he was standing prior to walking on the treadmill, his arterial pressure dropped to 60/44 mm. Hg. This rose to 84/72 mm. Hg when he was seated and tipped backward in a chair to enhance intrathoracic blood volume, but dropped again when he was sitting upright. Angiotensin II was reinfused, and within 3 minutes the arterial pressure rose to 170/106 mm. Hg while he was standing. He was able to walk at 1.7 miles per hour on a 10 per cent grade without difficulty, even though the infusion was again stopped. He had no symptoms after his blood pressure was raised with angiotensin II, and hypotension did not recur subsequently after exercise was discontinued. This demonstrated the therapeutic value of angiotensin II for symptomatic hypotension (due to inappropriate neurocirculatory regulation) as well as the capacity of the subject for exertion immediately after restoration of adequate blood pressure.

Discussion

In all studies on human subjects angiotensin II causes a significant increase in arterial pressure and systemic resistance. The effects on heart rate, cardiac index and stroke index are variable. In previous studies[1-4,14] (Table I), heart rate has been noted to fall consistently during infusions of angiotensin II, and this has been attributed to increased vagal tone mediated by the baroceptor reflexes incident to a rise in arterial pressure.[4,6] Although heart rate fell in 5 individuals in this study, there was an insignificant change in average heart rate. This is attributed to the faster heart rate in unsedated and somewhat apprehensive human subjects during cardiac catheterization. Stroke index and cardiac index fell significantly in this study (p = < .05 and < .02, respectively), in accord with the findings of Finnerty and associates, who studied normotensive patients, and also with Segel and associates.[3] Arteriovenous oxygen difference increased significantly in our subjects (p = < .01), whereas the cumulative average increase in previous studies was only about 0.6 volumes per cent (Table I). This discrepancy may reflect the heterogeneity of patients included in other studies.

In accord with previous reports, mean pulmonary arterial pressure rises 5 to 6 mm. Hg during continuous infusion of angiotensin II. Since this occurs after the rise in systemic arterial pressure, it may be the result of increased pressure in the pulmonary veins rather than the result of constriction of the arterioles proximal to the pulmonary capillaries. Nelson and associates[17] noted no change in the pulmonary arterial–pulmonary capillary pressure gradient in normotensive patients infused with natural angiotensin. Segel and associates[3] reported simultaneous increases in pulmonary arterial and systemic arterial pressures, but their published data show that pulmonary arterial pressure continues to rise slowly long after systemic pressure has reached a plateau. If angiotensin II indeed has no primary effect on the pulmonary vasculature, the observed increase in pulmonary arterial pressure may represent either a redistribution in blood volume to distend the blood vessels of the lung or altered distensibility of the left heart which elevates left ventricular end diastolic pressures. Indicator-dilution curves showed no increase in augmented

central blood volume but no measurements were made of left ventricular pressure or pulmonary blood volume.

Although it is generally agreed that venous pressure rises slowly during infusion of angiotensin II the existence of a primary constrictor effect on veins is controversial. Wood[11] found increased venous tone in normotensive subjects infused with angiotensin II but not in hypertensive subjects. If venous constriction is primary angiotension II is only half as potent as norepinephrine in this regard yet is several times as potent in constricting arterioles.[4,19,20]

Free fatty acid has an extremely rapid rate of turnover and is believed to be the most active metabolically of all blood lipids. In the fasting state, free fatty acid is the major energy producing substrate of striated muscle under conditions of aerobic contraction.[21] Whereas infusions of catechol amines increase arterial levels of free fatty acid by mobilization from fat depots,[22] no increase in arterial levels of free fatty acid occurred during infusion of angiotensin II. Since oxygen consumption and excess lactate (total body metabolism) did not increase, utilization of free fatty acid must have remained relatively constant. It is concluded that angiotensin II in the dosage and duration used does not influence mobilization or utilization of free fatty acid to a significant degree.

Summary

Ten normal male subjects were studied hemodynamically by cardiac catheterization during infusions of angiotensin II. Arterial levels of free fatty acid lactate pyruvate, and glucose were measured. Arterial pressure and the peripheral resistance index rose 31 and 68.8 per cent, respectively ($p = < 001$ for both). Cardiac index fell 23.5 per cent ($p = < 02$) and arteriovenous oxygen difference widened 25.3 per cent ($p = < 01$) in compensatory fashion since oxygen consumption did not change. Stroke index fell 20 7 per cent ($p = < 05$) and augmented central blood volume (3 subjects) fell slightly. The temperature of the skin fell as pressure rose and returned to normal concurrent with a fall in pressure after angiotensin was discontinued. No change occurred in coronary blood flow (3 subjects) or metabolic substrate levels. Pressures in the right atrium and pulmonary artery rose gradually several minutes after the rise in systemic arterial pressure. During supine leg exercise with angiotensin II (3 subjects) the peripheral resistance index did not rise as high as it had during rest which indicates that normal vasodilation of skeletal muscle still occurred in response to exercise. Reinfusion of angiotensin II was effective in one individual in the restoration of normal blood pressure after postinfusion hypotension.

REFERENCES

1 Page, I H and Bumpus, M Angiotensin Physiol. Rev 41:331 1961
2 Page, I H., McCubbin, J W Schwarz, H and Bumpus, M : Pharmacologic aspects of synthetic angiotensin, Circulation Res. 5:552, 1957
3 Peart, W S. Hypertension and the kidney II Experimental basis of renal hypertension, Brit. M J 2:1421 1959
4 Finnerty F A., Jr Massaro, G. DeC., Chupkovich, V and Tuckman, J Evaluation of the pressor cardiac, and renal hemodynamic properties of angiotensin II in man, Circulation Res. 9:256, 1961
5. Segel, N Harris, P., and Bishop, J M. The effects of synthetic hypertensin on the systemic and pulmonary circulations in man, Clin. Sc. 20:49 1961
6. Sancetta, S. M General and pulmonary hemodynamic effects of pure decapeptide angiotensin in normotensive man, Circulation Res 8:616, 1960.
7 Eckert, G. E., and Rose, J C. A study of angiotensin in the pulmonary circulation, Georgetown M. Bull 13 72, 1959
8. Maxwell, G M Castillo, C. A., Crumpton, C. W Clifford, J E and Rowe, G. G. The effect of synthetic angiotonin upon the heart of the intact dog, J Lab & Clin. Med 54:876 1959
9 Goodale, W T and Hackel, D B Measurement of coronary blood flow in dogs and man from rate of myocardial nitrous oxide desaturation, Circulation Res 1:502 1953
10 Barker S. B and Summerson, W H. Colorimetric determination of lactic acid in biological material, J Biol Chem. 138 138, 1941
11 Segal, S., Blair A E and Wyngaarden, J B. An enzymatic spectrophotometric method for the determination of pyruvic acid in blood J Lab & Clin. Med 48 137 1956.
12. Trout, D L., Estes, E H Friedberg S J Titration of free fatty acids of plasma a study of current methods and new modification J Lipid Res. 1 199 1960
13 Beach, E. F and Turner J J An enzymatic method for glucose determination in body fluids, Clin. Chem 4:462, 1958

14. Halsey, Y. Personal communication, 1960.
15. Huckabee, W. E.: Relationships of pyruvate and lactate during anaerobic metabolism. II. Exercise and formation of oxygen debt, J. Clin. Invest. 37:255, 1958.
16. Lichtlen, Von P., Buhlman, A., and Schaub, F.: Untersuchungen über die blutdrucksteigernde Wirkung von synthetischem Hypertensin II am normotonen Menschen, Cardiologia 35:139, 1959.
17. Nelson, R. A., May, L. G., Bennett, A., Kobayashi, M., and Gregory, R.: Comparison of the effects of pressor and depressor agents and influences on pulmonary and systemic pressures of normotensive and hypertensive subjects, Am. Heart J. 50:172, 1955.
18. Wood, J. E.: Absence of the normal peripheral venoconstrictor response to infusions of synthetic angiotensin II in patients with essential hypertension, J. Clin. Invest. 39:1040, 1960.
19. McQueen, E. G., and Morrison, R. B. I.: The effects of synthetic angiotensin and noradrenaline on blood pressure and renal function, Brit. Heart J. 23:1, 1961.
20. Kot, P. A., Cohn, J. N., Rose, J. C., and Freis, E. D.: Responses of veins and arteries to norepinephrine and angiotensin in the dog, Clin. Res. 9:141, 1961 (Abstr.)
21. Issekutz, B., Jr., and Spitzer, J. J.: Uptake of free fatty acids by skeletal muscle during stimulation, Proc. Soc. Exper. Biol. & Med. 105:21, 1960.
22. Bruce, R. A., Cobb, L. A., and Williams, R. H.: Effects of exercise and isoproterenol on free fatty acids and carbohydrates in cardiac patients, Am. J. M. Sc. 241:101, 1961.

A photoelectric approach to the study of peripheral circulation

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The application of photoelectric methods to the study of the peripheral circulation is not new. Approximately 20 years ago Hertzman applied this technique to the study of the blood volume pulse (BVP) and blood volume (BV) in the periphery by measuring the light intensity after transilluminating a limb or after reflecting the light from different areas of the skin.[11,12,13,14] Hertzman described his method as *photoelectric plethysmography*, a term which is justified only under certain conditions, as will be discussed later.

It is worth while to consider the factors which make such observations possible.

Cartwright[6] measured the transmission of light in a human cheek, 1 cm. thick, and found that in the 7 000 to 9 000 Å spectral region 1 per cent of the light was transmitted uniformly. At 6 000 Å the transmission fell almost to zero; it reached a maximum of 2 per cent approximately at 11,000 Å. In another instance,[7] he measured the transmission of light in fat (bacon) and found it to be four times more transparent in the same spectral region than was the human cheek. Similar results on human skin were obtained by Pauli and Ivančević.[26]

The same spectral band in which human tissue is transparent is extensively used in the measurements of absorption spectra of human oxygenated and reduced blood.[24,28] The extinction coefficient of human blood, especially in the nonhemolyzed state, is however much higher than that of the tissue.[29,31] One can expect, therefore, that when tissue is transilluminated by light in this spectral region or if such light is reflected from it, variations in the intensity of light, due to pulsating blood flow or vasomotor activity, will be observed.

Two additional crucial points must be considered: the light-source and the light detector.

There is no difficulty in obtaining a suitable source of light. Any incandescent lamp has an emission spectrum which covers the 7 000-9 000 Å band with a high light intensity (RCA Tube Handbook[28]).

The choice of a proper photodetector is a more difficult proposition. When Hertzman started his work on the photoelectric plethysmograph, barrier photocells were successfully introduced into another field closely connected with circulation, namely, oximetry.[24,25] However, in the study of peripheral circulation, barrier cells could not be used as light-detectors because their sensitivity in the 7,000 to 9 000 Å band is almost nil.

Therefore, Hertzman had to use as detectors photoemissive cells, which are big, unhandy, and insensitive. One can see from his papers[11,12] how difficult it was to

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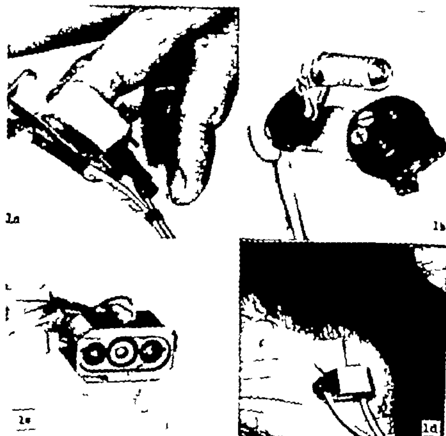


Fig. 1. Photocell-light assemblies (explanation in text.)

attach those detectors to the human body. Casts made of plaster of Paris had to be made individually for each subject to support photocell and light-source; the slightest movement between tissue and device marred the recordings, and many parts of the periphery were unaccessible.

These difficulties explain why no other workers tried to use this method as a research tool and why it never found its way into the clinic in spite of the fact that reliable transducers for the study of peripheral circulation are needed.

The advent of the photoconductive cells, especially the cadmium selenide (Hilger catalogue) and cadmium sulfide types (Mullard Technical Handbook[9]) changed the situation completely. These cells do not convert light energy directly into electrical current but vary their resistance under the influence of light; therefore, a special very simple circuit had to be assembled in order to convert these changes in resistance into fluctuating voltages that could be amplified to drive recorders.

The cells are very small—the FT 422 Hilger cell used in most of our experiments has an area of 1 mm.[2]—and their sensitivity in the spectral range required in our method is very high indeed: one to two amperes per lumen. The sensitivity of a barrier cell approaches only 0.3 mA. per lumen,[8] and, as mentioned above, its spectral range is completely inadequate.

Methods

Photocell assemblies. In a previous paper[11] we described our first attempts to use the photoconductive cell in the study of peripheral circulation. Further experiments taught us that the way in which the photocell and light-source are fastened to the part of the body to be investigated is of the utmost importance in eliminating artifacts. The simple solution offered[11] gave rise to difficulties in the interpretation of experiments because by fastening the photocell and light assembly with a small screw, we could not avoid a varying mechanical pressure on the fingertip or toe.

The method used by us now is much simpler and avoids those difficulties (Fig 1,*a*) Only adhesive tape is used but a hole is cut in it opposite the light-source, in order to avoid filtering and attenuation of the light—a feature which is not shown in the illustration

Photocell and light source are now one unit, and the hand arm or foot can be moved at will without interfering unduly with the recordings because the light falls always on the same part of the tissue.

The same method of attaching the photocell assembly can be used on the toe lobe of the ear and any part of the body which can be transilluminated. (A different device had to be built for recording the BVP in the pulp of a tooth)

Fig 1,*b* shows a device similar to the one in Fig 1,*a* but equipped with two cells and a common light-source. As will be explained later by connecting the output of one photocell circuit to an AC and the other to a DC amplifier BVP and changes in BV can be recorded simultaneously from two adjacent areas of tissue. Similar results can be obtained with one photocell connected to a DC and to an AC amplifier using a buffer stage to avoid interaction. We chose the first method because we found it easier to use two photocells than to construct a buffer stage.

To record BVP and changes in BV from any other part of the periphery where transillumination is not feasible, we use the device shown in Fig 1,*c* which records light scattered in the tissue.

Fig. 1,*d* shows how the device can be attached to any part of the body Light scattered in the tissue by the blood vessels reaches the photocell which is situated in the middle between two light-sources, and records of BVP and changes in BV can be obtained. The device shown in Fig 1,*c* contains only one photocell but two can be easily accommodated The two light bulbs are recessed but the photocell touches the surface of the skin.

In most of our experiments we used cadmium selenide cells manufactured by Hilger and Watts (Hilger catalogue) The types were FT 422 and FT 428. Recently we began experimenting with cadmium sulfide cells (Mullard Handbook) which have a similar sensitivity but a smoother spectral response curve. These cells are also small but are supplied in glass envelopes from which they have to be freed.

Photocell circuits Fig 2 shows the simple circuit used to convert changes in photocell resistance into fluctuating voltages

When the BVP was recorded the output from the resistor R was connected to an AC amplifier This resistor is of the same order as the average photocell resistance under the prevailing illumination When changes in BV were recorded the output was taken from the much smaller resistance r and connected to a DC amplifier The choice of a small r accounts for the larger signals which appear in this case because the changes in blood volume of the tissue, due to slow vasomotor action are generally larger than the change in blood volume which accompanies each pulse. Using a small r also brings the backing-off currents needed in DC recordings into the range provided by the backing off circuit of the amplifiers used by us (Grass 5 Pl. Low level DC preamplifier) Typical values of circuit components are given in Fig 2

All recordings in this paper were made with the above-mentioned equipment.

AC recording and *DC recording* designate the mode by which the preamplifier was used. The input impedance was 200 kilo-

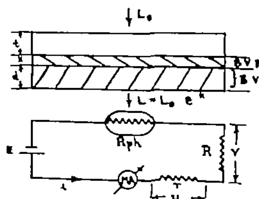


Fig 2 Schematic drawing of photocell circuit and transilluminated tissue. E = 22.5 V R = 15 K ohms. r = 100 ohms. R_{ph} = Average resistance of the photoconductive cell. = Output voltage L_o = Impingent light. L = Transmitted light. x = "Thickness" of blood volume pulse. d = "Thickness" of blood volume. t = "Thickness" of tissue without blood.

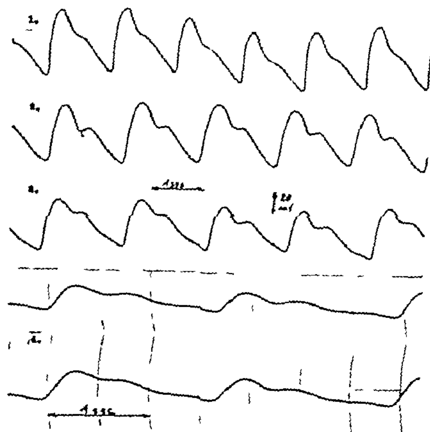


Fig. 3. Traces 1, 2, and 3 are finger blood volume pulses recorded with the photocell assembly shown in Fig. 1,a from three different subjects. AC recording time constant = 0.8 sec. Trace 4 is as those above but was recorded with the assembly shown in Fig. 1,b. The BVP was recorded simultaneously from two points on the same finger. AC recording time constant = 0.8 sec.

ohms in the AC mode and 20 kilo-ohms in the DC mode.

In AC recordings the output was always taken from *R*; in DC recordings it was taken from *r* (Fig. 2).

Results and discussion

The blood volume pulse. With the device shown in Fig. 1,a it is easy to record the BVP in the finger tip or in the toe. One gets the well known triangular curve form with a dicrotic notch on the descending part of the curve. Traces *1*, *2*, and *3* of Fig. 3 are such recordings obtained from three different subjects. Differences in the shape of the wave appear each time the same person is tested, but in general there is a certain regularity in the pattern of each subject. Unusual shapes often indicate some disorder in local or over-all circulation.[19]

An interesting observation was the disappearance of the dicrotic notch from the curve recorded from the finger tip when the arm was stretched. This fact may be of importance to the theories which explain the nature of this notch.[20]

There is no noticeable difference between recordings of BVP made from two points on the finger tip approximately half a centimeter apart. Fig. 3,4 shows traces recorded with the two-photocell assembly (Fig. 1,b) and one can see that the curves are similar, indicating that the photocell "sees" something common to a wider area of the tissue.

The shape of the BVP recorded by a mechanical finger plethysmograph[14] and that by the light plethysmograph are very similar,[15] although the two instruments record seemingly different phenomena—the mechanical plethysmograph

records changes in the volume of the limb whereas the light plethysmograph records changes in the transmittance of light in a part of the limb tissue. Actually there is no qualitative difference between the two recordings. The photocell "sees" the BVP only because of the fact that the amount of blood in the tissue undergoes rhythmical fluctuations the mechanical instrument records the fluctuations in volume in the finger tip for the same reason.

Theoretical basis of the photoelectric BVP recording Two important objections must be overcome before a claim can be made that the potential recorded across R (Fig 2) is a linear function of the rhythmically occurring fluctuations of BV in the vascular bed and that therefore, the light plethysmograph records a BVP shape which is identical to the one recorded by the mechanical finger plethysmograph

The first objection concerns the basic

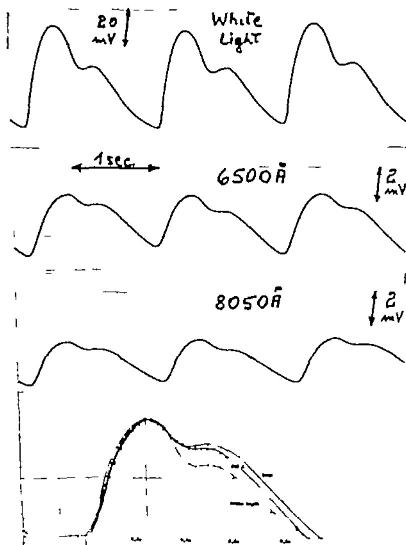


Fig 4 The upper three traces show recordings made from the finger tip of the same subject with white light and with 6,500 Å and 8,050 Å filters, respectively AC recording time constant = 0.8 sec. The composite figure is a normalized tracing of the first three curves (*650 Å* should read *6,500 Å*). The peak amplitude of each curve was arbitrarily set equal to 1 and all other amplitudes were scaled down accordingly The abscissa is marked in seconds.

relationship between impingent and absorbed light L_0 and L which is given by the Lambert Beer equation

$$L = L_0 \; e^{-\epsilon c d}$$

where ϵ is the extinction coefficient, c the concentration and d the layer thickness. This relationship was not derived for a nonhomogeneous flowing liquid (nonhemolyzed circulating blood) but the empirical measurements by Kramer[18] and Zijlstra[31] and the remarkable agreement of photoelectric oximetry in vivo[32] with the Van Slyke method demonstrated fairly well its approximate validity also in this case. In Fig. 2 *t* and *d* represent the thicknesses of the transilluminated tissue and the thickness of the BVP contained in it. Both can be assumed to be constant during the duration of a pulse stroke. *x* represents the additional blood volume due to the BVP. It is clear that one can write

$$L = L_0 \; e^{-\epsilon c (d + x)} = L \; A \; e^{-k}$$

where k = ϵ.c.x. is a function of *x* the blood thickness of the BVP because c is a constant and so is ϵ if the BVP is an arterial event only. According to this equation the light L falling on the photocell would be an exponential function of the BVP. This is not so because k < < 1 (see Appendix *I*). There are two reasons for this. The extinction coefficient both for oxygenated and reduced blood at 8,050 Å and above is relatively small[31,33] and our light-source is rich in light emitted in this spectral region (RCA Handbook). Therefore one can say that the measurements are made predominantly in this region. Also *x* the fluctuating blood-thickness due to the BVP in the finger tip is very small according to careful measurements made by Turner, Burch and Sodeman.[25]

Therefore the approximation

$$e^{-k} = 1 - k + \frac{k^2}{1 \cdot 2} - \cdots \sim 1 - k$$

can be made without introducing an appreciable error (Appendix *I*). It is shown in the Appendix that when this is accepted the voltage *v* measured across *R* (Fig. 2) and recorded by us is directly proportional to *x* the amplitude of the BVP.

The second objection to be overcome is the contention that the photoelectrically recorded BVP is weighted by the difference in the transmission of light by *arterial and venous blood or in other words*, that ϵ is not constant as was assumed above.[19]

It is possible that the BVP partly passes from the arterial to the venous side of the circulation as has been suggested by some workers.[3,4,6] Nobody has succeeded in giving a satisfactory answer to this objection. The great sensitivity of the photoconductive cell enabled us to use monochromatic light and thus to attempt a determination of the contribution of arterial and venous blood to the BVP observed in the periphery.

Fig. 4 shows the results of our experiments. *We recorded the BVP in the finger* tip of the same subject with white light and afterward through 6,500 and 8,050 Å monochromatic filters.

The choice of these filters was governed by the consideration that the difference between the extinction coefficients of oxygenated and reduced blood is largest at 6,500 Å and zero at 8,050 Å.[29] Since the interference filters at our disposal were big and heavy, our standard photocell assembly (Fig. 1,*a*) could not be used. The finger tip was put on the photocell—in this case a cadmium sulfide cell ORP 11. Above the photocell were the filter and light-source. Thus there was no rigid connection between finger, photocell and light-source and this made the recordings difficult.

One can see from Fig. 4 that the recordings made with monochromatic light differ considerably from the one made with white light. The dicrotic notch moved nearer to the peak and became less marked. The difference between the monochromatic recordings is not so striking. When similar recordings were made on subjects whose dicrotic notch was small the monochromatic records became rounded off and the dicrotic notch could hardly be seen.

To facilitate the analysis of the experiments, we redrew the three curves, normalizing them—bringing them up to the same maximal amplitude (Fig. 4 *bottom*).

One can see that in the normalized tracings the three curves are almost completely overlapping until the peak of the BVP is reached. After the peak there is a considerable difference between the recordings made with white light and those made with monochromatic light and a smaller one between each of the monochromatic traces.

In order to apply to these results the line of reasoning used by workers dealing with photocell oximetry[23] one has to work with light-source photocell and filters which are calibrated. Although this was not done in the experiments which are reported some important conclusions can be drawn.

It seems that the part of the BVP before the peak is a monochromatic event and therefore, the amplitudes of the traces made with different monochromatic wavelengths differ by constants only. These were found by arbitrarily setting the maximal amplitudes of the BVP of each record to 1. After the peak a new event sets in which is seen differently by the two monochromatic beams and therefore also by the white light. What we call a monochromatic event could be also a mixed arterial venous pulse in which the ratio of the arterial and venous components remains constant. One should not forget that, although the normalized traces in Fig. 4 give a qualitatively correct picture of the nonmonochromatic part of the BVP the quantitative separation of these curves after the peak is also a function of the light-source photocell and filter constants (Appendix, J)

These experiments, although not yet conclusive, seem to us to be very promising and probably will throw new light on an important aspect of peripheral circulation.

The BVP made with an 8,050-Å monochromatic filter (Fig. 4) is of special interest. Under these conditions the photoelectric plethysmograph does not distinguish between oxygenated and reduced blood and the record obtained should be identical in shape with the one obtained from a mechanical finger-plethysmograph. Therefore, we could use in this case the term *photoelectric plethysmography* to describe the method.

Our experience shows that a simple infrared filter Agfa 850 gives traces which are almost identical with those observed when we used an 8 050-Å interference filter. This can be explained by the fact that at wavelengths greater than 8 050 Å the difference between the extinction coefficients of oxygenated blood and those of reduced nonhemolyzed blood is probably not great and their ratio almost constant (up to 9 000 Å approximately) as established for hemolyzed blood.[24,25] A Wratten 88A filter behaves similarly to an Agfa 850 filter.

It was assumed that the isobestic point for oxygenated and reduced blood is at 8 050 Å. This is true not only for hemolyzed blood[24,25] but also for nonhemolyzed blood with which we are concerned here.[26] Should the method be applied in animal experiments, the different optical behavior of animal blood will have to be considered.[24]

The BVP recorded with scattered light. The photoelectric approach to the study of peripheral circulation would be very much limited if only transilluminated limbs could be studied even though transillumination can be applied to quite unexpected parts of the body. For instance we succeeded in recording in this way the BVP in the pulp of a tooth. Dr. Erb of our Dental School helped us to prepare the dental plate which held the photocell and light source.

Where transillumination is impossible light scattered in the skin or reflected from it can be utilized. We used the scattering approach and recordings obtained in this way from different parts of the body are shown in Fig. 5. The device developed for this purpose was the one shown in *c* and *d* of Fig. 1. The bulbs are recessed and do not touch the skin and the photocell touches it as explained previously.

The curves obtained from the areas specified in Fig. 5 are different in shape from those obtained by transillumination of the finger tip or toe. The dicrotic notch appears on a different part of the curve nearer the peak. This seems to be a mechanical or optical property of the BVP in these parts of the body and not of the way the recordings were made because the BVP from the finger tip has always the same characteristic shape shown in Fig. 3 whether the recording was made

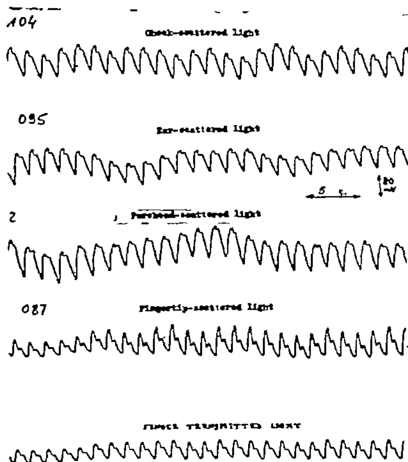


Fig 5 BVP recorded with scattered light. Recordings made with the photocell-light assembly shown in and *d* of Fig 1 AC recording Explanation in text

by light passing through the finger tip or scattered in it It is worth while to note that the amplitudes of the signals obtained with light scattered in the skin are considerably larger than those obtained by transillumination using the same light source.

Some measurements carried out on medical students from Africa showed that both methods—transmitted and scattered light—can be used even when the skin is heavily pigmented without producing *an appreciable attenuation of recorded* signals.

Recordings of blood volume. The photoelectric method enables one not only to follow the BVP in any part of the periphery but provides a *convenient method* for the observation of peripheral vasomotor activity In this case we have to deal with two variables—the rhythmical BVP and the slower sometimes periodical changes in volume caused by constriction or *dilatation of* blood *vessels in the* vascular bed.

Two examples of such recordings were chosen one is concerned with the influence of a gravitational stimulus (lifting of arm) *and the other shows the influence of deep* breathing (Fig 6)

Fig 6,*a* shows a recording obtained when the arm was lifted from a position below heart level to one above it. The photocell *assembly shown in Fig 1,a was on the* finger tip. The output to the recorder (DC amplifier) was taken from the resistor *r* (Fig 2) When the arm was in the lower position (left part of Fig 6,*a*) the backing *off circuit of the amplifier* was used to bring the pen into the position shown on the record. The amplification is such that the amplitude of the BVP is small When

the arm is lifted the BV in the finger tip drops (more light reaches the photocell) but the BVP increases—although not at once—and then the level of BV recovers partially

The experiment probably illustrates a local regulatory mechanism which maintains blood flow by dilatation of vessels as was suggested by Turner Burch and Sodeman.[11] A simultaneous recording made on the finger tip of the other resting hand showed almost no changes in BV and BVP

Exactly the same results were obtained when a foot was lifted The subject was seated with the photocell on the toe the foot was on the floor and then was raised to a horizontal position. The result of this experiment contradicts the opinion expressed by Martin[12] that such a local regulatory effect does not exist in the toe.

During some experiments the changes in BV were so large that an amplification had to be chosen in which the shift on the base line connected with changes in BV was recorded but not the BVP because its amplitude was too small In such cases the double photocell assembly shown in Fig 1,*b* can be used and changes in BV and BVP recorded on two separate traces (Fig 6,*b*) from the same finger tip. The great difference in the sensitivities of the amplifier settings (0.5 mV./cm. and 20 mV./cm.) in the recording of the traces in Fig 6,*b* is due to the different size of the resistors across which the respective outputs were taken (see Fig 2)

Work is in progress (with the Third Internal Clinic Hadassah Hospital Jerusalem) in which a gravitational stimulus is applied to subjects suffering from Raynaud's disease or acrocyanosis. When the arm is lifted the BVP behaves differently in both diseases (acrocyanosis as in normal subjects) It seems, therefore, that the simultaneous observation of the BVP and changes in BV which occur under these conditions may be of diagnostic value and of some help in understanding the functional disturbances which underlie the cause of these diseases.

The deep breathing experiment (Fig 6,*c*) shows that one deep inhalation of air is followed by a vasoconstriction in the finger tip Here both BV and BVP decrease, a response which is different from that seen in Fig 6,*a*

Since the recordings in Fig 6 show both the BVP and changes in the BV they represent therefore, a combined sphygmogram and plethysmogram obtained from the same extremity

Recordings of BV which have been discussed up until now were made with light transmitted through the finger tip. They were made also with scattered light from most areas of the skin with the photocell assembly shown in Fig 1,*c* with equal ease.

One may be asked whether the changes in BV which occur during such experiments could be estimated The approximation proposed when the BVP was considered is not applicable because the h[illegible] in "blood thickness" are too great

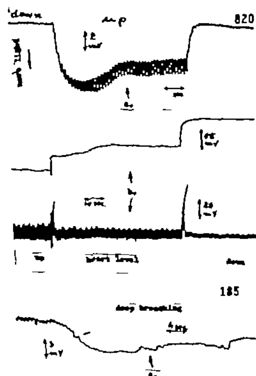


Fig 6 Recordings of blood volume. *a*, Changing position of arm with photocell assembly of Fig 1,*a* on finger tip. Explanation in text. DC recording *b* Changing position of arm with photocell assembly of Fig. 1,*b* on finger tip. *Upper trace*. DC recording *Lower trace*. AC recording Time constant = 0.1 sec. *c* Deep breathing. Two photocell assemblies of Fig. 1,*a* on two finger tips of different hands. *Upper trace* DC recording *Lower trace* AC recording Time constant = 0.8 sec. Explanation in text.

One way of estimating the changes in BV would be to express them in BVP amplitudes which appear as can be seen on the same record (Fig. 6,a). The other more quantitative way would be to calculate the photocell resistance, *Rph* for both positions of the limb. This can be done easily because the measured signal is $i \cdot r$ where i is the current in the photocell circuit (Fig. 2). Since all of the electrical parameters are known i and therefore, *Rph* can be calculated. From the photocell characteristic one can read the light amplitudes connected with each *Rph*. With the help of the Lambert Beer equation the ratio of the "blood thicknesses" in both positions of the limb can be obtained (see Appendix 2). However the answer will always be how many times the BV is larger or smaller than in a previous position of the limb but never in absolute BV quantities. If such measurements are attempted the photocell must be calibrated. A proper filter as explained above, should be used to be sure that the measurements are color independent.

Without doubt this method of calibrating the photoelectric plethysmographic recordings would be superior to the one proposed by Hertzman and Dillon[13] using glass filter units." It will be dependent, however on the applicability of the Lambert Beer equation to whole blood. This was already discussed above. Kramer and associates,[27] who investigated this problem carefully came to the conclusion that in spite of the "complex and variable optical properties" of whole blood the possibility of a quantitative basis for oximetry in vivo cannot be excluded a priori and deserves further investigation.

Other applications. It should be clear from what has been said up to now that the photoelectric technique described in this paper lends itself easily to the study of the reflex controls of the cutaneous circulation—reactions to cold heat pain etc. We have performed many such experiments. By measurement of both parameters, BV and BVP and their time dependence on different parts of the periphery a better understanding of the regulatory processes can be obtained.

Venous-occlusion experiments can also be easily performed and recorded.[31]

This report would be incomplete if it did not mention the study of psychosomatic phenomena related to peripheral circulation.[3] It was reported that visual auditory and tactile stimuli evoke constriction of vessels in the finger tip and dilatation on the surface of the head.[32] These are probably brought about by the orienting reflex, the motor component of which is accompanied by changes in heart rate and respiration.[33] We observed this reflex as characteristic anticipatory actions—the raising of the BVP before a subject raised his arms when he anticipated the order. These and many other interesting phenomena which are often mentioned but never thoroughly investigated can now be attacked easily. As an example, we would like to mention the method developed by Luria and Vinogradova,[32] wherein changes due to the orienting reflex which occur in the peripheral vascular bed are used to study the dynamics of the semantic system—the connection between word complexes as they are stored in the memory. In these investigations the simple photoelectric technique is very useful and should replace the mechanical devices used by the authors.

Conclusion

The photoelectric method described in this paper lends itself easily to the study of events in the peripheral circulation in man. It is one of the research methods which enables the investigator to measure parameters under almost normal physiologic conditions. The small measuring devices developed by us can be fitted at the same time to different parts of the body without interfering unduly with conditions which existed before the experiments were begun. Therefore these devices should facilitate the study of vasomotor regulation and autonomic reflexes which control the peripheral circulation. The method has its limitations. It is a dynamic method—it measures changes only. For instance, it can answer the question of how much the blood volume (BV) in the finger tip or in many other parts of the periphery increases accepting an arbitrary zero level and of how rapidly this change occurs but it cannot measure the absolute amount of change in the blood volume. Despite

these limitations it can in our opinion open new research avenues, give satisfactory answers to many outstanding problems,[14,27] and serve as a useful diagnostic tool in the clinic.

The paper as presented here is concerned mainly with testing the validity of the proposed method. We went into the functional interpretation of the experiments performed only in order to show the potentialities inherent in the method. Each of the problems touched on by us should be investigated separately.

Summary

Living tissue is transparent to red and infrared radiation in the spectral range at which measurements of extinction coefficients of oxygenated and nonoxygenated blood are generally made. The extinction coefficient of nonhemolyzed blood in this region is much higher than that of the tissue. Incandescent lamps are cheap sources of these wavelengths, and photoconductive cells are extremely sensitive detectors.

Therefore if tissue is illuminated by light in this spectral region one can expect to be able to detect the varying amount of blood in the tissue due to pulsating flow and vasomotor action.

To convert changes in resistance of the photoconductive cells to voltages, simple electrical circuits had to be devised.

Photocells and light-sources are built into one small unit which can be easily attached to any part of the body. Light passing through the tissue or scattered in it can be detected.

Because of the high sensitivity of the cells light filters can be used and changes in flow due to venous or arterial blood can be studied.

Experiments were performed in order to test the validity of the proposed method.

We are indebted to Professor J. Magnes and the staff of the Department of Physiology for valuable advise and criticism and for the permission to use their recorder. The photocell assemblies used by us were made in the Mechanical Workshop of the Hebrew University Medical School under the supervision of Mr. E. Jechezkely.

REFERENCES

1. Burch, G. E.: A new sensitive portable plethysmograph, Am. Heart J. 33:48, 1947.
2. Burch, G. E., and Ray, T.: Cardiovascular system as the effector organ in psychosomatic phenomena, J. A. M. A. 136:1011, 1948.
3. Burch, G. E.: A method for recording and a study of the venous occlusive technique, etc. 1954 (see p. 38 of Reference 27).
4. Burch, G. E.: Selective quantitative applications of digital rheoplethysmography, Am. Heart J. 52:388, 1956.
5. Burch, G. E.: Private communication, 1961.
6. Burton, A. C.: A critical survey of methods available for the measurement of human peripheral flow. 1954 (see p. 16 of Reference 27).
7. Cartwright, C. H.: Infrared transmission of the flesh, J. Ophth. Soc. Am. 20:81, 1930.
8. Cartwright, C. H.: Spectral transmission of human body. *In* Glaser, O., editor: Medical physics, vol. 1, Chicago, 1944, Year Book Publishers, Inc., p. 1157.
9. Cannon, C. G.: Electronics for spectroscopists, London, 1960, Hilger Watts, Ltd., p. 263.
10. Davis, D. L., and Hertzman, A. B.: The analysis of vascular reactions in the nasal mucosa with the photoelectric plethysmograph, Ann. Otol. Rhin. & Laryng. 66:622, 1957.
11. Hertzman, A. B., and Spielman, C. R.: Observations on the finger volume pulse recorded photoelectrically, Am. J. Physiol. 119:334, 1937.
12. Hertzman, A. B.: Photoelectric plethysmography of the nasal septum, Proc. Soc. Exper. Biol. & Med. 37:290, 1937-1938.
13. Hertzman, A. B.: The blood supply of various skin areas as estimated by the photoelectric plethysmograph, Am. J. Physiol. 124:328, 1938.
14. Hertzman, A. B.: Vasomotor regulation of cutaneous circulation, Physiol. Rev. 39:280, 1959.
15. Hertzman, A. B., and Dillon, J. B.: The applications of photoelectric plethysmography in peripheral vascular disease, Am. Heart J. 20:750, 1940.
16. Hertzman, A. B., and Dillon, J. B.: Reaction of large and small arteries in man to vasoconstrictor stimuli, Am. J. Physiol. 130:56, 1940.
17. Haden, R. L.: Hemoglobinometry. *In* Glaser, O., editor: Medical physics, vol. 1, Chicago, 1944, Year Book Publishers, Inc., p. 600.
18. Hilger Watts, Ltd.: Catalogue C. M. 357/3.
19. Kramer, K.: Ein Verfahren zur fortlaufenden Messung des Sauerstoffgehaltes im stromenden Blute an uneroffneten Gefassen, Ztschr. Biol. 96:61, 1935.
20. Kramer, K., Elam, J. O., Saxton, G. A., and Elam, W. N.: Influence of oxygen saturation, erythrocyte concentration and optical depth upon the red and near-infrared light transmittance of whole blood, Am. J. Physiol. 165:229, 1951.
21. Luria, A. R., and Vinogradova, O. S.: An objective investigation of the dynamics of the semantic system, Brit. J. Psychol. 50:89, 1959.
22. MacDonald, D. A.: Blood flow in arteries, London, 1960, Edward Arnold, Ltd.
23. Martin, P.: Some aspects of functional disorders of the circulation, 1954 (See p. 204 of Reference 27).

24. Matthes, K., and Gross F. Untersuchungen über die Absorption von rotem und ultrarotem Licht durch kohlenoxydgesättigtes, sauerstoff gesättigtes und reduziertes Blut, Arch. exper Path. u. Pharmakol. 191:369 1939

25. Mullard technical handbook, vol. 4 Semiconductor and photoelectric devices.

26. Pauli, W. E., and Ivančević, I. Untersuchungen über das Absorptionsvermögen der Haut im langwelligen Gebiet des Spektrums Strahlentherapie 23:537 192

27. Peripheral circulation in man, Ciba Foundation symposium, London, 1954, Churchill, Ltd.

28. Radio Corporation of America tube handbook, ol. 3-4

29. Robinson, I and Gantt, W. M. The orienting reflex, Bull. Johns Hopkins Hosp. 80:231 1947

30. Stoermer J Die Bedeutung arterieller Pulskurven für die kardiologische Diagnostik im Kindesalter Arch Kinderh. 161:22, 1960

31. Turner R. H., Burch G E., and Sodeman, W. A. Some effects of raising and lowering the arm upon the pulse volume and blood volume of the human finger tip in certain diseases of the blood vessels, J Clin. Invest. 16:789 1937

32. Weinman, J., Bicher C., and Levy D.: Application of a photoconductive cell to the study of peripheral circulation in limbs of animal and man, J Appl. Physiol. 15:317 1960.

33. Wood, E. H., Sutterer W F and Cronin, L. In Glaser O., editor: Medical physics, vol. 3 Oximetry Chicago 1960 Year Book Publishers, Inc.

34. Zijlstra, W. G Fundamentals and applications of clinical oximetry Assen, Holland, 1953 Van Gorcum

35. Zijlstra W. G A manual of reflection oximetry Assen, Holland, 1958, Van Gorcum.

Appendix

I The blood volume pulse amplitude The fluctuations in the light which reaches the photocell during the BVP (Fig 2) can written as Equation (1) (*see below*) g that ε, the extinction coefficient the concentration and d and t are constants. Equation 1 can also be written as shown in Equation (2) (*see below*) where $k = \epsilon \cdot c \cdot x$.

The total blood volume in the finger tip according to Turner and associates[31] amounts to 100 mm.³ (average of 33 normal subjects) and the BVP is 2 8 per cent of it. This permits us to calculate the maximal "blood-thickness" (x) of the BVP (area of the finger tip assumed to be 200 mm.²) as 0 0014 cm.

The molecular extinction coefficient (c = 1 mM/l d = 10 mm.) for hemolyzed blood at the 8 050 Å isobestic point is known.[34] Taking into account the concentration c of whole blood[17] and the fact that we are dealing with nonhemolyzed blood[24] the ε of which is considerably greater we get

$$k = \epsilon \cdot c \cdot x = 0.017 << 1$$

Therefore Equation 2 can be approximated to

$$\Delta L = L_0 A k = L_0 A \epsilon c x = B x \qquad (3)$$

The voltage measured by an AC amplifier which is receiving its input from R (Fig 2) will give Equation (4) (*see below*) because $\Delta R_{ph} << R_{ph}$.

This was found to be true in all of our measurements (ΔR_{ph} = 400 ohms when R_{ph} = 50 K ohms are representative values)

R_{ph} is the average photocell resistance and therefore, a constant, and ΔR_{ph} is

*The capital letters A, B, C, D, F G designate constant quantities.

$$\Delta L = L_1 - L_2 = L_0 e^{-\epsilon c (d+t)} - L_0 e^{-\epsilon c (d+t+x)} = L_0 A (1 - e^{-\epsilon c x}) \qquad (1)$$

$$\Delta L = L_0 A (1 - e^{-k}) = L_0 A \left(1 - 1 + k - \frac{k^2}{1 \cdot 2} + \quad \right) = L_0 A \left(k - \frac{k^2}{2} + \quad \right) \qquad (2)$$

$$v = i R = \frac{E}{R + R_{ph}} - \frac{E}{R + R_{ph} + \Delta R_{ph}} \sim \frac{F \Delta R_{ph}}{(R + R_{ph})^2} \qquad (4)$$

the change in photocell resistance due to the BVP Therefore Equation 4 can be written as

$$v = C \quad \Delta R_{ph} \qquad (5)$$

For small changes in photocell resistance Δ Rph and small fluctuations in light Δ L, Δ Rph = D Δ L. Therefore from Equation 5

$$v = C \quad \Delta R_{ph} = C \quad D \quad \Delta L = C \quad D \quad B \quad x$$

or

$$v = \text{constant } x$$

which means that the voltage measured across R in Fig 2 is, to a great approximation a linear function of the BVP

2 Calculation of changes in blood volume Looking at Fig 2 one can write Equation (6) (*see below*) where L_1 and L_2 are the light intensities reaching the photocell during a change in the BV thickness from d_1 to d_2 x the BVP is neglected because we are measuring now the shift of the BV base line only Therefore

$$d_1/d \;=\; lnL_1/lnL_2 \qquad (7)$$

Measuring $v_1 = i_1 \quad r$ and $v_2 = i_2 \quad r$ (Fig 2) and knowing all other circuit constants we can calculate R_{ph1} and R_{ph2} Knowing R_{ph1} and R_{ph2} one can obtain from the photocell characteristic the values of L_1 and L_2 in arbitrary units and calculate d_1/d_2 from Equation 7

3 BVP recorded with monochromatic light The spectral distribution of the light source and the spectral response of the photocell are usually functions of the wavelength After proper correction factors have been introduced Equation (8) (*see below*) for the light reaching the photocell can be written where ε is the extinction coefficient for oxygenated and reduced blood at 8,050 and 6,500 Å respectively $x_a(t)$ and $x_b(t)$ are the volume pulse of the arterial and venous components and L is the impingent light. (The equations for the photocell currents would differ from Equation 8 by a constant only)

Our experiments show that by multiplying Equations 8a and 8b by a constant (normalization) we can make the amplitudes $I_{8\,050}$ and $I_{6\,500}$ equal over a period of time Looking at Equations 8a and 8b one can see that this is possible only if one of the variables, $x_a(t)$ or $x_b(t)$ is equal to zero or if their ratio remains constant

$$\left.\begin{aligned} L &= L_0 \quad e^{-(d+x)} = L_0 \quad F \quad e^{-} \quad = G \quad e^{-} \\ L_2 &= L_0 \quad e^{-(\;+d_2)} = L_0 \quad F \quad e^{-d} \quad = G \quad e^{-} \end{aligned}\right\} \qquad (6)$$

$$ln\, I_{8\,050} = \varepsilon^{HbO_2}_{8\,050} \quad c \quad x_a(t) + \varepsilon^{Hb}_{8\,050} \quad c \quad x_b(t) + ln\, L_{8\,050} \qquad (8a)$$

$$ln\, I_{6\,500} = \varepsilon^{HbO_2}_{6\,500} \quad c \quad x_a(t) + \varepsilon^{Hb}_{6\,500} \quad c \quad x_b(t) + ln\, L_{6\,500} \qquad (8b)$$

An intracardiac sound generator for the study of the transmission of heart murmurs in man

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Although in past and recent years many studies were devoted to the mechanism of production of heart sounds and murmurs,[1] the process of transmission of cardiac vibrations from their inner sources to the surface of the body has received rather poor attention and our present knowledge on the matter is still based largely on empirical observations. Yet the process of transmission is of fundamental importance in determining the physical characteristics and localization of cardiovascular sound on the surface of the chest.

During the transmission of sound there is absorption, reflection, refraction, resonance, selective attenuation, and conduction at different velocities through the structures which surround the heart, with the final result that what we hear or record on the chest is not a true representation of the vibratory phenomena which originated within the heart. At times the process of transmission may affect cardiovascular sound to such an extent that pathologic features are completely masked and can be detected only by means of intracardiac or direct epicardial recordings. Some examples of this kind are the continuous murmur of small patent ductus arteriosus,[2-4] *the soft delayed pulmonary component of* the second sound in severe pulmonary stenosis,[5] and the presystolic murmur at the tricuspid valve in atrial septal defect with left-to-right shunt.[6] Other similar observations were made by the author in four years of experience with simultaneous intracardiac and external phonocardiographic recordings.[6-11] Intracardiac phonocardiography, however, appears to be rather inadequate for the study of the transmission of sound mainly because of the great diversity *of the intracardiac pickup in comparison* with the external microphones.

Therefore, a new method of investigation was conceived.[12] This consists in delivering an acoustical signal of known characteristics directly within the chambers of the heart. This signal is then recorded from the surface of the body, and the modifications of its frequency, intensity, quality, and duration, due to the process of transmission, are easily detected.

This study was devoted particularly to some aspects of the transmission of heart murmurs. Therefore, a small water turbine placed at the tip of a catheter was used as a generator of sound. The noise produced by the turbine is very similar to a cardiac murmur, both in its physical characteristics and mechanism of production.

This study was presented in part at the 22nd Congress of the Società Italiana di Cardiologia held at Sanremo, Italy, June 23-25, 1961.

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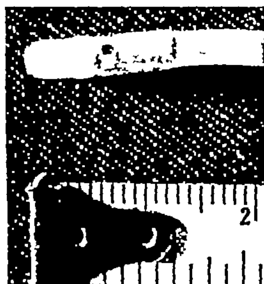


Fig 1 The tip of the turbocatheter

Methods

The sound generator is a metallic turbine incorporated into the tip of a polyethylene tubing which has an internal diameter of 2.5 mm (Fig 1) The case of the turbine is cylindrical (Fig 2) It has a diameter of 2.5 mm and a length of 7 mm. The turbine is of the axial flow or propeller type. Its runner has four blades and rotates under the impulse of a flow of normal saline delivered through the polyethylene tubing Since the characteristics of the noise produced by the turbine depend mainly upon the rate of flow of saline, this was controlled through the use of an automatic injector

The saline solution leaves the turbine through four holes which are situated on the lateral wall of the case at the level of the runner blades

The ensemble of the turbine and plastic tubing which is termed *turbocatheter* was introduced into the cavities of the right side of the heart and the pulmonary artery by means of the usual technique of venous catheterization The tip of the turbocatheter which incorporates the metallic turbine is clearly visible on the fluoroscope The body of the catheter can be made radiopaque by filling it with contrast medium (Fig 3) Localization of the turbine within the heart is possible by fluoroscopy and by pressure readings easily obtained through the turbocatheter

The acoustical signals were delivered by the turbine at multiple sites within the right atrium right ventricle pulmonary artery and venae cavae as shown in Fig 4

The frequency components of the artificial murmurs were between 80 and 360 cycles per second with predominance of the higher frequencies. The intensity lower at the beginning and at the very end of the murmurs was rigorously kept the same for all signals produced in the same subject This was made possible by the use of the automatic injector and was proved by delivering two or more signals in the same place and obtaining identical records from the same areas on the surface of the chest The duration of the artificial murmurs ranged between 1 20 and 1 80 seconds

The recordings from the surface of the chest were made by means of two or more microphones which were applied simultaneously not only on the cardinal points of auscultation but also in several other areas.

To provide more precise localization of sound recordings contact microphones which were designed to explore areas up to 1.5 cm in diameter were used The micro-

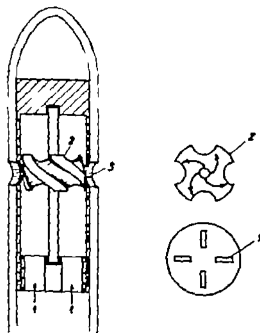


Fig 2 Diagram of the intracardiac turbine 1 Inlet 2 Runner 3 Outlet



Fig 3 The tip of the turbocatheter is lying within the left pulmonary artery Two microphones are applied externally on the aortic and pulmonary areas.

phones were fed into a six-channel photographic recorder (Hellige Multicardiotest) which by selective filtration splits the sounds into five frequency bands which correspond partly to those suggested by Maas and Weber [11] In this study the following bands were used 70 to 140, 140 to 250 and 250 to 500 cycles per second All phonocardiograms were recorded at a paper speed of 50 mm per second and at a constant electronic amplification.

Fifteen patients whose ages ranged from 18 to 26 years were selected for this study All underwent routine cardiac catheterization for diagnostic purposes. Two of them had small atrial septal defects four had mild mitral stenosis one showed an unexplained moderate rise in pulmonary pressures and in the other eight the catheterization findings were within normal limits. The heart was not significantly enlarged in any of the patients.

Results

Figs. 5 to 8 show some examples of artificial murmurs produced within the right ventricle and right atrium Each section of recording shows actually two phonocardiograms (obtained from two different areas) separated by an electrocardiogram

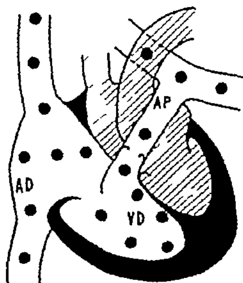


Fig 4 Diagram showing the multiple sites at which artificial murmurs were delivered. AP Pulmonary artery VD Right ventricle. AD Right atrium.

which was used as a reference tracing. The upper phonocardiogram is split into two frequency bands: 140 to 250 (first line) and 250 to 500 cycles per second (second line). The lower phonocardiogram is split into three frequency bands: 70 to 140 (first line), 140 to 250 (second line), 250 to 500 cycles per second (third line).

In Fig. 5 a murmur delivered in the inflow tract of the right ventricle near the tricuspid valve is well transmitted to the third and fourth right intercostal spaces where it is recorded with equal intensity and duration. This murmur is rather poorly transmitted to the fourth left intercostal space and not recorded at all in the third left intercostal space. It should be noted that in the transmission of this murmur to the fourth left intercostal space the higher frequency vibrations have disappeared to a great extent, whereas low-frequency vibrations are still present.

In Fig. 6 (upper tracing) an artificial murmur produced within the right ventricle in the region of the apex is well recorded from the fifth right intercostal space but is much less evident in the fifth left intercostal space. It is quite remarkable that this same acoustical signal when delivered from the middle part of the right atrium (Fig. 6, lower tracing) is almost completely dissipated during the transmission and is not appreciable in multiple recordings from the surface of the chest.

Figs. 7 and 8 show some recordings of signals produced in the upper and lower parts of the right atrium and demonstrate that murmurs which originate within the right atrium are rather poorly transmitted to the surface of the chest.

Discussion

Since the early decades of the last century murmurs were produced artificially by compression of a vessel (Corrigan[14] 1829) or in models (Savart[15] 1830) for the purpose of studying the mechanism of production of cardiovascular sound. Never to

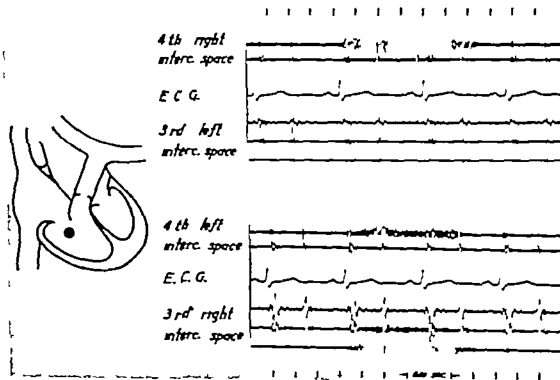


Fig. 5. An artificial murmur delivered from the inflow tract of the right ventricle, as shown in the diagram, is well transmitted to the fourth and third right intercostal spaces; it is transmitted with less intensity to the fourth left intercostal space and not transmitted at all to the third left intercostal space. (For more explanation and the values of the frequency bands of the phonocardiograms, see text.)

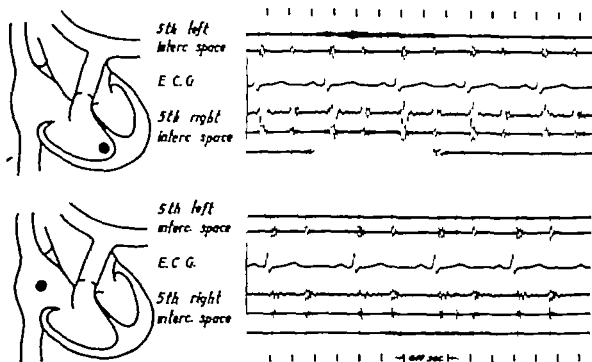


Fig. 6. The same artificial murmur has been delivered from the right ventricle (near the apex) and the middle of the right atrium as shown in the diagrams. When delivered from the right ventricle, the murmur is well transmitted to the surface of the chest; when delivered from the atrium, it is almost completely dissipated during transmission. (The frequency bands of the phonocardiograms are given in the text.)

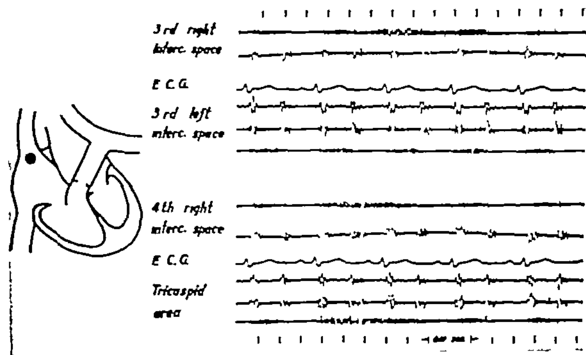


Fig. 7. A murmur delivered *from the upper part* of the right atrium is poorly transmitted to the chest, where it is best recorded from the third and fourth right intercostal spaces and the tricuspid area.

the best of my knowledge, have murmurs been produced artificially within the chambers of the heart in man for the purpose of investigating the transmission of cardiovascular sound.

The murmurs produced by the technique described herein have parameters which are very similar to those observed in the diseased heart. Furthermore, the mechanisms of production of the two types of murmurs have some factors in common. It is known that heart murmurs are caused mainly by turbulent flow, cavitation phenomena, and vibrations of cardiovascular structures. In miniature, these phenomena occur at the tip of the turbocatheter where the turbine transforms the flow of saline into a turbulent flow, produces vibrations due to unbalance of rotating parts, and causes cavitation in the fluid which surrounds the runner, as do all propellers.[13] However, the main cause of the noise produced by the turbocatheter is the rotating blades, which create periodic changes in pressure in the liquid which surrounds the runner. These periodic changes in pressure constitute a source of sound waves. The sound waves which originate from different points around the runner blades interact with each other and produce a composite noise pattern whose main frequency is equal to the angular speed (number of rounds per second) times the number of blades.[14] By means of this simple calculation it is possible to derive the main frequency of the noise produced by the turbocatheter.

The intensity of the artificial murmurs was not calibrated in this preliminary study. However, as mentioned above, by means of automatically controlled injections the intensity was kept the same for all signals delivered in the same subject while the electronic amplification of the recording system was constant. In this manner it was possible to compare the

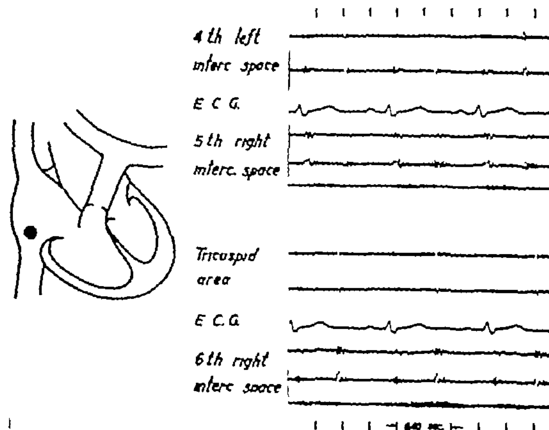


Fig. 8. A murmur delivered from the lower part of the right atrium is very poorly transmitted to the chest, where only a few vibrations of high frequency are appreciable in the sixth right intercostal space.

intensity of the multiple phonocardiograms recorded from the chest.

Even though the type of acoustical signals used in this investigation resemble rather closely the real sounds of the heart, and therefore, make easy the comparison with the conditions of the living heart, more accurate calibration of the intensity and frequency of the signals is needed. With this aim in mind, we are studying new intracardiac generators of sound of the electromagnetic type in this laboratory.[17] These generators will provide acoustical signals of controlled intensity and frequency.

The preliminary results presented show some striking features. Signals of equal intensity, frequency, and quality produced within the right ventricle and the right atrium have a clear-cut different behavior: those from the right ventricle are easily transmitted to the surface of the chest, whereas those from the right atrium are almost completely dissipated during the process of transmission. Another interesting observation which confirms a rather [illegible]on notion is that the high frequencies predominate in the epicenter of the area of transmission, whereas the lower frequencies predominate at the periphery.

These are only a few observations which barely give an idea of the amount of information to be obtained by this technique not only in the realm of basic studies but also in that of clinical phonocardiography.

Summary

A new technique for the study of the transmission of cardiovascular sounds in man is described. The technique consists in delivering an acoustical signal of known characteristics directly within the chambers of the heart. This signal is then recorded from the surface of the chest and the modifications of its parameters due to transmission are detected.

In this preliminary study a small water turbine incorporated into the tip of a catheter was used as a generator of sound. Sounds produced by the turbine, which rotates under the impulse of a flow of normal saline are similar in their physical characteristics and mechanism of production to the murmurs produced in the diseased heart.

Some examples of transmission of murmurs produced artificially at multiple sites within the right ventricle and right atrium are given.

REFERENCES

1. Rushmer, R. F., Kelly, J. J., Jr., Kuo, P. T., McDonald, D. A., Lewis, D. H., and Rodbard, S.: Symposium on cardiovascular sound. Part I. Mechanisms, Circulation 16:270, 1957.
2. Lewis, D. H., Deitz, G. W., Wallace, J. D., and Brown, J. R.: Intracardiac phonocardiography in man, Circulation 16:764, 1957.
3. Feruglio, G. A.: Primi rilievi di fonocardiografia intracardiaca nelle cardiopatie congenite, Friuli med. 13:1068, 1958.
4. Feruglio, G. A., Dalla Volta, S., Lewis, D. H., and Wallace, J. D.: La phonocardiographie intracardiaque chez l'homme, Arch. mal. coeur 52:1156, 1959.
5. Feruglio, G. A.: Intracardiac phonocardiography: a valuable diagnostic technique in congenital and acquired heart disease, AM. HEART J. 58:827, 1959.
6. Feruglio, G. A., and Sreenivasan, A.: Intracardiac phonocardiogram in thirty cases of atrial septal defect, Circulation 20:1087, 1959.
7. Feruglio, G. A.: Rilievi di fonocardiografia intracardiaca nell'uomo, Proceedings of the 20th Congress of the Italian Society of Cardiology, *Rimini, 1958, Vol. 2,* p. 485.
8. Feruglio, G. A., and Gunton, R. W.: Intracardiac phonocardiography in ventricular septal defect, Circulation 21:49, 1960.
9. Feruglio, G. A., Gunton, R. W., Sreenivasan, A., and Hennebecker, R. O.: Intracardiac phonocardiography in some complicated cardiac problems, Am. Surg. 152:29, 1960.
10. Feruglio, G. A.: Sul valore diagnostico del *fonocardiogramma intracardiaco,* Minerva med. 51:?, 1960.
11. Feruglio, G. A.: Tre anni di esperienza con la fonocardiografia intracardiaca, Proceedings of the 3rd European Congress of Cardiology, Rome, 1960, Vol. 2, p. 665.
12. Maass, H., and Weber, A.: Herzschallregistrierung mittels differenzierender Filter: Eine Studie zur Herzschallnormung, Cardiologia 21:773, 1952.
13. Corrigan, D. J.: Inquiry into the cause of "bruit de soufflet" and "frémissement cataire," Lancet 2:1 and 33, 1829.
14. Savart, F.: On some acoustic phenomena produced by the motion of liquids through short efflux tubes, Phil. Mag. ?:186, 1834.
15. Bochi, G.: Le moderne turbine idrauliche, Milan, 1957, Ulrico Hoepli, p. 56 and p. 328.
16. Binder, R. C.: Fluid mechanics, ed. 3, Englewood Cliffs, N. J., 1956, Prentice-Hall, Inc., p. 376.
17. Feruglio, G. A.: Preliminary studies with an intracardiac generator of sound in the investigation of the transmission and calibration of heart sounds and murmurs, Proceedings of the 22nd Congress of the Italian Society of Cardiology, San Remo, 1961 (In press.)

The effects of intravenous guanethidine on the systemic and pulmonary circulations in man

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Since the introduction of guanethidine in the treatment of arterial hypertension there have been numerous accounts of its clinical effectiveness and limitations. However despite the increasing use of the drug there is still a very limited knowledge concerning its effects on the systemic and pulmonary circulations in normal or hypertensive human subjects. A brief preliminary report of the hemodynamic changes after acute parenteral administration of the drug in 5 hypertensive patients was made by Taylor and Donald (1960) [1] In the present report the effects of the intravenous administration of the drug on the systemic and pulmonary circulations of both normal subjects and hypertensive patients at rest and during graded exercise are considered in detail

The interpretation of many of the previous investigations of the circulatory effects of guanethidine in hypertensive patients is rendered difficult by the possible presence of secondary damage to the heart kidneys, and other organs in the patients studied For this reason all the hypertensive subjects selected for this investigation were apparently fit and leading a normal active life

Methods

Clinical data Observations were made on 4 normal subjects and 12 patients with essential arterial hypertension of varying degrees of severity The sex age height, weight and surface area of these 16 subjects are detailed in Table I Patients GH 1-6 were suffering from moderate hypertension (resting mean aortic pressure of 130 to 150 mm Hg) whereas Patients GH 7-12 were suffering from more severe arterial hypertension (resting mean aortic pressure of 150 to 200 mm. Hg) Patients GH 1 2 4 6 7 8 and 10 were referred to us after the incidental discovery of a high arterial pressure during routine

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medical or insurance examinations. Of the other 5 patients all were suffering only from headaches when referred and none had any symptoms of cardiac or vascular insufficiency.

A family history of arterial hypertension was present in Patients GH 1, 2, 4, 6, 7, 8, and 10; hypertension was discovered during early pregnancy 7 years previously in Patient GH 9. No patient had any clinical signs of cardiac insufficiency, and in all the size of the heart as estimated clinically and radiologically was within normal limits. However, in 7 (Patients GH 3, 6, 7, 8, 10, 11, and 12) of the 12 hypertensive patients the radiologic cardiac configuration suggested left ventricular hypertrophy without dilatation. There was electrocardiographic evidence of left ventricular preponderance in 4 (Patients GH 7, 10, 11, and 12) of the 12 hypertensive patients, and in the others there was no electrocardiographic abnormality. The optic fundi were normal or showed only mild arterial changes in all the hypertensive patients; in none was there papilledema, hemorrhages, or exudates. Microscopy of the urine showed it to be normal and the urine was sterile to culture in all patients. Nine-hour urinary concentration tests, blood urea, and 24-hour creatinine clearance tests were within normal limits in all patients. None had proteinuria and the intravenous pyelogram was normal in all instances. The 24-hour urinary catecholamine excretion was normal in the 6 hypertensive patients (Patients GH 1, 3, 4, 7, 9, and 10) in whom it was carried out. The blood hemoglobin concentration and sedimentation rate were within normal limits in all patients.

Plan of investigation. Previous training was instituted to familiarize the subjects with the bicycle ergometer, investigative procedure, and laboratory surroundings. The studies were then carried out with the patient in the fasting state in the morning some days later. After the venous and arterial catheters were positioned under radiologic screening control, a period of 30 minutes was allowed for the patient to achieve a basal state before observations were commenced. All subjects were studied in the supine posture at rest, during light leg exercise on the constant-speed variable load ergometer for 6 minutes, and during consecutive moderate leg exercise for an additional 6 minutes. After this 12 minutes of continuous exercise the subject was required to lie quietly, and recovery observations were made between the sixteenth and twentieth minutes after the cessation of exercise. A control Valsalva maneuver (40 mm. Hg for 15 to 20 seconds) was then carried out and immediately afterward guanethidine was injected slowly at a constant rate of 1 to 2 mg. per minute into a catheter in the axillary vein. The dose of drug administered varied from 10 to 40 mg. between different subjects. The injection was given over a period of 10 to 20 minutes during which time the aortic blood pressure was continuously recorded. Sufficient drug was given to cause an appreciable fall in the mean aortic blood pressure. After completion of the injection a variable period of time was allowed to elapse until the repeated Valsalva maneuver showed unequivocal evidence of complete block of vasoconstriction and absence of arterial pressure overshoot; this period varied from 30 to 60 minutes after the completion of the injection of the drug. After the demonstration of adequate sympathetic blockade, the studies were repeated in an identical manner. A diagrammatic representation of the plan of investigation is shown in Fig. 1.

Cardiac outputs were determined by the Fick method, and intravascular pressures were recorded at the same time during periods of 4 minutes at rest and recovery and during a period of 2 minutes during exercise (*vide infra*). The resting observations, made during the period of 4 minutes, were completed 1 minute before the commencement of exercise. The exercise observations were made during the fifth and sixth minutes of light exercise (oxygen uptake range 309-544 ml. per minute per square meter) and again during the fifth and sixth minutes of moderate exercise (oxygen uptake range 439-756 ml. per minute per square meter). The recovery observations were made between the sixteenth and twentieth minutes after exercise ceased. After the drug had been given the observations were repeated in an identical manner over the same periods. During any given period of observation

mean phasic, and in the case of the pulmonary circulation differential pressures were recorded synchronously at recording paper speeds of 16 mm. per second and 80 mm. per second alternately. Samples of blood of 3 ml. were taken at evenly spaced intervals throughout each period of observation: four from the pulmonary artery for determination of oxygen saturation, and three from the aorta for determinations of oxygen saturation and blood oxygen capacity.

In order to determine the effect of any changes in the plasma volume contributing to the hemodynamic alterations produced by the drug, repeated measurements of the total circulating blood volume were made by means of a standardized radioalbumin dilution technique in 2 of the hypertensive patients (Patients GH 6 and GH 8). The blood volume was measured during the rest and recovery periods both before and after the drug, a total of four determinations of blood volume was made in each patient.

Laboratory techniques. The laboratory air temperature was controlled at 68 to 70 degrees Fahrenheit in all studies; the relative humidity varied between 45 and 60 per cent between different studies, but never more than 3 per cent during the course of a single investigation. A 9F double lumen catheter was positioned under radiologic screening control with the tip in the pulmonary wedged position, usually in a lateral or basal segment of the right lung. The pulmonary wedged position was confirmed by study of the wave-forms from the tip of the catheter which were contrasted with those recorded synchronously from both the pulmonary artery and the aorta. Sampling from the tip was usually not possible, but when successful completely oxygenated blood was obtained. The proximal side orifice of the catheter was in the main stem or proximal part of the right main pulmonary artery; a distance of 17 cm. between the orifices of the catheter was used to ensure this. A 7F or 8F single-lumen catheter was positioned in the axillary vein of the opposite arm, 2 cm. lateral to the first rib, for the purpose of sampling the axillary venous blood (regional circulatory studies are being reported in a separate paper) and the drug was injected through this catheter. A 50-cm. Odman catheter with an internal diameter of 1 mm. was passed percutaneously by a modified Seldinger procedure (over 0.8 mm. nylon threaded through a Riley arterial needle) into the brachial artery and positioned under screening control in the ascending portion or arch of the aorta.

Aortic pressures were transduced by a Statham P23D strain gauge with a predetermined hydraulic damping setting for the catheter-manometer system at approximately 0.7 of its critical damping frequency. The square-wave response of this catheter-manometer system was 95 per cent within 0.03 second, with less than 5 per cent overshoot. The frequency response of the whole saline-filled system was recorded by means of a variable-speed sine wave pump immediately at the end of each investigation; the response was virtually flat to a range of 20 to 25 cycles per second depending on the batch of material from which the individual catheters were made. Pulmonary wedged and arterial pressures were applied without additional damping to opposite chambers of a New Electronic Products (N.E.P.) differential manometer of inductance type. Although the square wave and frequency responses of this system were relatively poor, it still allowed accurate mean and direct differential pressures to be recorded. Zero reference level

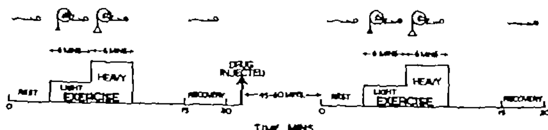


Fig. 1. Diagrammatic representation of the plan of investigation.

of all the manometers was 10 cm above the plane of the x-ray table the manometer heads were fixed at this level The electrical output from the manometers was arranged to allow synchronous recording of both the pulsatile and mean venous and aortic pressures over the same calibration range All pressures and an electrocardiographic trace (*Lead CR*$_1$) were recorded on an N.E.P. ultraviolet light recorder with a limiting frequency response of 5 000 cycles per second which was arranged to utilize only the linear range of the galvanometers and arc of traverse of the ultraviolet light beams. Venous pressure channels were calibrated from zero against open saline columns. The systemic arterial calibration was arranged to extend approximately 5 to 10 mm Hg on either side of the aortic pulse pressure to allow maximum recording precision with the least electromechanical distortion The saline filled calibration pressure heads for this system were maintained by specially calibrated Reckla aneroid manometers.

Measurements of pulsatile and mean pressure were made throughout the period of observation except when samples of blood were being taken Mean venous pressures were determined by electrical integration the systolic and diastolic pulmonary arterial pressures reported were measured in the end-expiratory phase Aortic pressures recorded at a paper speed of 80 mm per second were measured planimetrically over a minimum of 20 pulses and the mean pressure was checked against that measured by electrical integration The systolic and diastolic aortic pressures reported are the average of the 20 values measured from the same 20 pulses which were used to obtain the planimetric mean

Expired air was collected in a Tissot spirometer until the collected volume exceeded the minimal dilution factor of 21 liters In all instances the air was collected immediately before the period of observation and discarded just prior to the start of the collection of expired air for analysis. Duplicate samples of gas were analyzed in duplicate on separate Scholander gas apparatus by two different observers, and the duplicates of each sample were required to check to 0 03 per cent Analysis of room air was carried out in each case immediately prior to commencement of the analysis of expired air and the range of oxygen concentrations accepted varied between the limits of 20 93 and 20 98 per cent oxygen

The percentage of oxygen saturation of the samples of blood was estimated by a modified procedure using a Brinkman hemoreflector The hemoreflector technique was standardized by calibration against both the Van Slyke manometric method and a spectrophotometric technique employing a Unicam SP 600 densitometer After withdrawal the samples of blood were immediately analyzed in duplicate and required to check to 0 5 per cent saturation The blood oxygen capacity was measured by a standard photometric technique on a Unicam SP 600 which was calibrated against the Van Slyke method ($r = 0.990$) When these techniques are used serial determinations of resting cardiac outputs by the Fick method agree within a total range of 5 per cent

The total circulating blood volume was determined by means of the plasma volume corrected for the hematocrit The plasma volume was measured by the injection of 3 to 5 microcuries of radioiodinated human serum albumin diluted in 20 ml of freshly constituted human plasma through the catheter in the axillary vein Samples of blood were taken from the aorta at intervals of 5 8 and 10 minutes and centrifuged The radioactivity of exactly 4 ml of the resulting plasma was measured in a well scintillation counter coupled to an automatic timer over a period of 400 seconds Duplicate counts were required to check to less than 1 per cent The standard solution prepared from the original dilution of radioalbumin was corrected for dropped counts. Extrapolation of the three points to zero time was judged to give the circulating plasma volume at this time The hematocrit was measured by centrifuging 2 ml of whole blood at 3 000 r p m for 30 minutes.

Calculation of the vascular resistances In the traditional calculation of the systemic vascular resistance of a subject the mean aortic blood pressure which is relatively constant in health is divided by the cardiac output which is a direct function

of body size and surface area. Thus, the larger a normal subject is the smaller is the systemic vascular resistance. The relative consistency of the aortic blood pressure in health is due to the number of parallel arteriolar resistances (resistance varies inversely to this number) and the cardiac output both are a direct function of body size. It will be clear from these considerations that the traditional calculation of systemic vascular resistance is greatly affected by body size, and its meaning in terms of arteriolar caliber is ambiguous. However if the systemic vascular resistance in the body mass equivalent to 1 square meter (sq M) of surface area is considered then

$$\underset{(\text{sq M})}{\text{Systemic vascular resistance}} = \frac{\text{Mean Aortic Blood Pressure}}{\text{Blood flow/sq.M}}$$

$$\underset{(\text{dynes sec. cm.}^{-5}\text{ sq M})}{\text{Systemic vascular resistance}} = \frac{\text{Mean Aortic Blood Pressure (mm Hg)} \times 1{,}332 \times 60}{\text{Cardiac index (ml./min./sq.M)}}$$

Thus the calculation of the systemic vascular resistance per unit body mass eliminates the effect of increasing numbers of parallel resistances in the larger person and a figure is obtained which gives a more accurate assessment of the state of the systemic arterioles. The units are similar to those in the more commonly used calculation. The same argument may be applied to the calculation of the pulmonary vascular resistance

Results

The individual observations for each subject are detailed in Table I The mean values of these observations, together with the standard error of the mean and standard deviation of observations, are given in Table II Description of significant or nonsignificant differences between groups is based on orthodox statistical methods (Fisher 1945) [3]

A comparison of the circulatory effects of the drug in the resting state presents some difficulty In spite of prior familiarization of the subjects with the laboratory and its personnel and although 30 minutes were allowed to elapse between positioning of the catheters and the commencement of the initial resting studies these attempts to ensure a basal state were only partially successful The cardiac output pulse rate ventilation and respiratory rate recorded in the pre-exercise resting studies were often considerably higher than those recorded during the period 16 to 20 minutes after the first 12 minute period of exercise. It is a matter of common observation that patients who are stimulated by any experimental procedure can be brought to a more basal and stable state by a short period of light exercise and subsequent recovery The reasons for this are no doubt multiple and complex but it is probable that the main factors are psychological Because the patients were more stable and basal during the first period of recovery and because the drug was administered immediately after these observations had been recorded it was considered that the comparison of these recovery observations with those of the immediately subsequent postinjection resting period afforded the most reliable data concerning the effects of the drug at rest In the subsequent discussion, therefore, the observations at rest before and after the drug refer to the preinjection recovery and the postinjection resting periods, respectively

Respiratory rate and ventilatory minute volume The individual values of the respiratory rate and ventilatory minute volume of the normal subjects and hypertensive patients at rest before and after guanethidine are shown in Fig 2 Although there was considerable individual variation in both groups of subjects of the resting respiratory rate before and after guanethidine the average values for each group before and after the drug were not significantly different (Table II) Likewise, the average respiratory rates at similar levels of exercise and oxygen uptake before and after the drug were not significantly different in

Table I Hemodynamic effects of guanethidine—individual observations in 4 normal subjects

Subject Sex Age / B.A. (sq. M.) / Height (M.) / Weight (Kg.)	State	Respiratory rate (per min.) Before	After	Ventilation B.T.P.S. (L./min./sq. M.) Before	After	Respiratory quotient Before	After	Oxygen uptake S.T.P.D. (ml./min./sq. M.) Before	After	Blood oxygen capacity (Vol. %) Before	After	Blood oxygen saturation (%) Arterial Before	After	Mixed venous Before	After	A-V difference (Vol. %) Before	After	Cardiac output (L./min./sq. M.) Before	After	Heart rate (per min.) Before	After
GN 1	Rest	13	12	3 [illegible]	4 18	0 77	0 81	[illegible]	131	19 69	19 12	[illegible]	[illegible]	73 7	74 0	4 18	4 41	3 [illegible]	3 46	74	74
M 26	Ex. I	18	17	7 05	7 [illegible]	0 76	0 85	418	[illegible]	20 31	19 13	96 0	[illegible] 0	80 0	[illegible] 0	7 31	7 [illegible]	5 73	4 [illegible]	105	91
1 62	Ex. II	17	20	12 [illegible]	14 80	0 [illegible]	0 [illegible]	632	[illegible]	20 27	19 10	96 0	96 1	87 0	[illegible] 1	6 81	9 [illegible]	7 41	0 78	127	111
1 [illegible]	Recy	11	17	3 81	4 05	0 [illegible]	0 [illegible]	[illegible]	187	19 70	19 [illegible]	97 3	[illegible] 0	77 0	73 3	4 80	4 [illegible]	3 97	3 37	76	74
[illegible] 3																					
GN 2	Rest	11	9	7 87	9 29	0 [illegible]	0 [illegible]	224	223	18 90	18 81	[illegible] 9	[illegible] 8	65 8	83 0	4 [illegible]	8 23	4 [illegible]	4 36	[illegible]	90
M 29	Ex. I	13	16	6 84	7 [illegible]	0 79	0 [illegible]	487	416	16 73	18 81	96 4	93 6	49 0	42 8	6 12	8 03	5 78	5 [illegible]	121	108
1 91	Ex. II	17	16	13 [illegible]	11 [illegible]	0 78	0 [illegible]	871	[illegible]	18 90	18 [illegible]	[illegible] 5	93 9	30 8	33 6	9 05	9 74	5 [illegible]	6 31	130	118
1 75	Recy	8	9	6 51	7 21	0 [illegible]	0 80	[illegible]	218	18 [illegible]	14 70	97 1	91 8	61 2	80 6	8 47	8 02	3 71	4 19	[illegible]	[illegible]
71 8																					
GN 3	Rest	17	18	6 67	5 70	0 97	0 70	170	108	18 17	18 27	[illegible] 5	[illegible] 1	73 6	72 5	4 80	4 [illegible]	3 [illegible]	3 61	72	78
M, 24	F I	13	13	7 [illegible]	13 84	0 80	0 78	[illegible]	428	19 11	18 78	[illegible] 8	97 3	65 3	61 5	6 47	6 72	6 18	6 37	84	[illegible]
1 90	Ex. II	13	14	14 30	20 42	0 [illegible]	0 [illegible]	413	[illegible]	19 61	18 [illegible]	97 3	[illegible] 3	30 9	51 4	8 [illegible]	7 [illegible]	7 31	7 18	117	91
1 [illegible]	Recy	18	16	6 14	6 48	0 87	0 70	178	189	18 97	16 [illegible]	[illegible] 3	[illegible] 0	73 5	71 9	4 65	4 70	3 78	3 89	[illegible]	81
70 8																					
GN 4	Rest	19	10	7 83	10 60	0 [illegible]	0 81	108	133	19 36	17 [illegible]	97 4	97 6	73 7	73 1	4 14	4 18	4 06	4 07	67	79
M [illegible]	Ex. I	18	15	7 48	8 [illegible]	0 71	0 73	377	[illegible]	19 16	18 11	97 1	[illegible] 4	[illegible] 7	[illegible] 6	6 97	7 17	5 40	5 [illegible]	85	81
1 [illegible]	Ex. II	19	16	13 73	14 74	0 [illegible]	0 [illegible]	[illegible]	[illegible]	19 82	18 10	[illegible] 0	96 4	[illegible] 6	[illegible] 8	6 11	8 34	7 36	7 08	[illegible]	[illegible]
1 78	Recy	11	10	9 01	8 [illegible]	0 93	0 81	214	177	18 [illegible]	17 [illegible]	[illegible] 5	97 6	73 6	73 9	4 83	4 25	4 41	4 17	71	80
[illegible] 4																					

Table I—Cont'd Hemodynamic effects of guanethidine—individual observations in 12

Patient Sex, Age / B.A. (sq. M.) / Height (M.) / Weight (Kg.)	State	Respiratory rate (per min.) Before	After	Ventilation B.T.P.S. (L./min./sq. M.) Before	After	Respiratory quotient Before	After	Oxygen uptake S.T.P.D. (ml./min./sq. M.) Before	After	Blood oxygen capacity (Vol. %) Before	After	Blood oxygen saturation (%) Arterial Before	After	Mixed venous Before	After	A-V difference (Vol. %) Before	After	Cardiac output (L./min./sq. M.) Before	After	Heart rate (per min.) Before	After
GH 1	Rest	9	11	4 33	5 [illegible]	0 82	0 83	101	104	18 [illegible]	19 13	[illegible] 9	97 4	73 4	[illegible] 6	4 [illegible]	5 31	4 18	3 44	87	[illegible]
M, 31	Ex. I	13	14	10 72	9 [illegible]	0 [illegible]	0 [illegible]	488	441	19 [illegible]	19 [illegible]	[illegible] 6	[illegible] 5	87 9	[illegible] 5	7 [illegible]	7 45	6 47	6 49	81	79
1 71	Ex. II	18	19	12 [illegible]	13 [illegible]	0 83	0 [illegible]	[illegible]	370	19 47	18 [illegible]	[illegible] 4	95 5	83 3	87 2	8 [illegible]	8 20	7 [illegible]	6 79	97	80
1 [illegible]	Recy	13	18	6 29	4 23	0 90	0 84	[illegible]	176	19 43	18 [illegible]	97 2	[illegible] 0	[illegible] 5	85 4	6 41	8 18	3 43	3 [illegible]	67	[illegible]
63 5																					
GH 2	Rest	9	9	3.36	3 41	0 61	0 80	[illegible]	147	21 [illegible]	[illegible] 22	[illegible] 8	[illegible] 0	72 4	72 8	3 36	4 45	3 [illegible]	3 31	71	85
M, 40	Ex. I	18	16	8 78	8 14	0 81	0 76	[illegible]	[illegible]	21 21	20 43	94 9	91 8	65 6	82 7	6 85	6 30	6 17	6 30	112	112
1 97	Ex. II	11	12	11 41	[illegible] 30	0 83	0 81	[illegible]	[illegible]	22 23	21 [illegible]	93 6	82 4	39 0	83 6	7 [illegible]	6 40	7 [illegible]	6 61	120	122
1 79	Recy	9	8	3 17	3.[illegible]	0 95	0 82	137	133	21 45	20 [illegible]	94 5	94 5	71 5	70 6	4 [illegible]	5 31	2 73	2 95	71	79
[illegible] 0																					

Stroke volume (ml./sq. M.)		Right atrial		Vascular pressures (mm. Hg): Pulmonary arterial: Systolic		Diastolic		Mean		Pulmonary wedge (mean)		Aortic: Systolic		Diastolic		Mean		Vascular resistance (dynes sec. cm.⁻⁵ sq. M.): Pulmonary		Systemic	
Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
[illegible]	[illegible]	8	—	[illegible]	[illegible]	13	13	18	14	11	8	134	165	84	71	[illegible]	[illegible]	103	141	2,201	[illegible]
58	54	—	—	24	38	[illegible]	19	34	21	17	13	147	122	93	78	118	[illegible]	[illegible]	117	1 619	[illegible]
[illegible]	[illegible]	—	—	34	34	16	21	[illegible]	24	16	16	130	[illegible]	[illegible]	[illegible]	123	110	[illegible]	107	[illegible]	1 304
43	46	—	8	23	[illegible]	13	11	17	18	9		125	109	[illegible]	74	101	[illegible]	173	141	[illegible]	2,134
[illegible]	47	6	—	24	[illegible]	18	18	17	[illegible]	8	[illegible]	[illegible]	[illegible]	77	73	[illegible]	[illegible]	[illegible]	112	[illegible]	[illegible]
[illegible]	45	—	—	23	31	[illegible]	22	24	24	19	11	173	[illegible]	[illegible]	71	119	[illegible]	[illegible]	115	[illegible]	[illegible]
[illegible]	57	—	—	31	34	[illegible]	24	23	[illegible]	14	11	171	144	[illegible]	73	119	[illegible]	[illegible]	190	[illegible]	[illegible]
40	[illegible]	—	6	[illegible]	24	13	[illegible]	14	17	8	8	134	[illegible]	[illegible]	[illegible]	100	[illegible]	[illegible]	119	[illegible]	[illegible]
[illegible]	47	3	—	23	[illegible]	14	12	[illegible]	13	[illegible]	6	121	[illegible]	[illegible]	[illegible]	91	78	120	113	[illegible]	1 719
[illegible]	73	—	—	33	[illegible]	18	18	24	21	18	13	137	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	73	[illegible]	1 319	[illegible]
[illegible]	78	—	—	23	29	18	[illegible]	[illegible]	[illegible]	14	12	148	112	[illegible]	[illegible]	104	80	47	112	[illegible]	[illegible]
47	43	—	3	23	19	14	13	18	13	9	6	178	[illegible]	77	[illegible]	[illegible]	73	148	[illegible]	[illegible]	[illegible]
61	[illegible]	4	—	23	24	14	14	13	12	[illegible]	[illegible]	172	[illegible]	78	61	113	[illegible]	[illegible]	31	2,311	[illegible]
[illegible]	[illegible]	—	—	[illegible]	[illegible]	13	17	24	19	17	13	[illegible]	[illegible]	47	[illegible]	137	103	181	[illegible]	[illegible]	[illegible]
71	74	—	—	[illegible]	29	23	19	23	22	18	12	207	[illegible]	[illegible]	[illegible]	142	[illegible]	91	114	[illegible]	1,206
61	[illegible]	—	4	22	21	13	11	18	12	11	[illegible]	164	[illegible]	79	[illegible]	114	[illegible]	72	[illegible]	[illegible]	[illegible]

hypertensive patients

Stroke volume (ml./sq. M.)		Right atrial		Vascular pressures (mm. Hg): Pulmonary arterial: Systolic		Diastolic		Mean		Pulmonary wedge (mean)		Aortic: Systolic		Diastolic		Mean		Vascular resistance (dynes sec. cm.⁻⁵ sq. M.): Pulmonary		Systemic	
Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
[illegible]	[illegible]	5	—	[illegible]	[illegible]	[illegible]	13	18	15	8	7	[illegible]	178	113	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
77	77	—	—	41	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	14	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	111	171	[illegible]	[illegible]
75	74	—	—	[illegible]	[illegible]	19	[illegible]	22	21	11	8	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
84	[illegible]	—	5	[illegible]	[illegible]	[illegible]	13	17	16	7	7	[illegible]	[illegible]	130	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	47	6	—	[illegible]	[illegible]	21	18	27	[illegible]	14	11	174	[illegible]	[illegible]	[illegible]	131	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	—	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	17	[illegible]	[illegible]	113	117	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	—	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	31	18	13	[illegible]	[illegible]	113	94	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
37	[illegible]	—	6	34	24	[illegible]	13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	130	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table I—Cont'd Hemodynamic effects of guanethidine—individual observations in 12

Patient Sex, Age B.A. (sq. M.) Height (M.) Weight (Kg.)	State	Respiratory rate (per min.) Before	Respiratory rate (per min.) After	Ventilation B.T.P.S. (L./min./sq. M.) Before	Ventilation B.T.P.S. (L./min./sq. M.) After	Respiratory quotient Before	Respiratory quotient After	Oxygen uptake S.T.P.D. (ml./min./sq. M.) Before	Oxygen uptake S.T.P.D. (ml./min./sq. M.) After	Blood oxygen capacity (Vol. %) Before	Blood oxygen capacity (Vol. %) After	Blood oxygen saturation (%) Arterial Before	Blood oxygen saturation (%) Arterial After	Blood oxygen saturation (%) Mixed venous Before	Blood oxygen saturation (%) Mixed venous After	A-V difference (Vol. %) Before	A-V difference (Vol. %) After	Cardiac output (L./min./sq. M.) Before	Cardiac output (L./min./sq. M.) After	Heart rate (per min.) Before	Heart rate (per min.) After
GH 3	Rest	22	23	4.73	4.80	[illegible]	[illegible]	170	180	20.31	[illegible]	[illegible]	[illegible]	73.3	[illegible]	4.37	[illegible]	[illegible]	2.87	71	[illegible]
M, 44	Ex. I	22	27	10.67	10.27	[illegible]	[illegible]	373	384	[illegible]	[illegible]	[illegible]	[illegible]	87.3	[illegible]	7.43	7.[illegible]	5.08	4.84	[illegible]	71
2.01	Ex. II	23	23	16.67	13.87	[illegible]	0.91	430	434	[illegible]	20.79	93.7	97.2	84.9	84.3	8.13	[illegible]	5.40	[illegible]	87	73
1.73	Recy	19	15	5.14	4.08	[illegible]	0.[illegible]	164	138	21.[illegible]	20.12	[illegible]	97.2	70.8	67.[illegible]	4.[illegible]	[illegible]	2.20	2.27	[illegible]	[illegible]
[illegible]																					
GH 4	Rest	23	23	5.65	[illegible]	0.78	[illegible]	185	207	19.28	18.70	94.0	[illegible]	[illegible]	67.7	4.[illegible]	6.23	2.[illegible]	3.[illegible]	84	[illegible]
M, 48	Ex. I	[illegible]	[illegible]	10.85	11.36	[illegible]	[illegible]	[illegible]	418	19.92	18.[illegible]	[illegible]	93.4	64.2	40.4	7.78	6.18	[illegible]	[illegible]	97	[illegible]
1.67	Ex. II	25	25	16.43	14.82	0.91	[illegible]	615	630	20.[illegible]	19.66	94.4	[illegible]	46.3	43.9	[illegible]	[illegible]	[illegible]	[illegible]	110	113
1.78	Recy	20	20	3.87	12.08	0.82	[illegible]	207	222	19.36	18.67	[illegible]	[illegible]	[illegible]	61.7	5.[illegible]	[illegible]	3.[illegible]	3.00	[illegible]	100
[illegible]																					
GH 5	Rest	18	20	4.60	6.20	[illegible]	[illegible]	138	142	19.62	19.14	[illegible]	[illegible]	74.7	70.3	4.[illegible]	3.00	3.41	3.64	[illegible]	[illegible]
M, 39	Ex. I	18	24	8.78	10.38	[illegible]	0.[illegible]	300	400	[illegible]	19.18	96.4	94.6	63.1	[illegible]	6.79	6.44	4.[illegible]	[illegible]	104	111
1.80	Ex. II	22	20	14.78	13.40	[illegible]	[illegible]	507	[illegible]	[illegible]	19.14	96.1	[illegible]	[illegible]	43.4	8.74	7.96	[illegible]	7.12	123	134
1.[illegible]	Recy	21	20	4.73	6.[illegible]	[illegible]	[illegible]	140	143	16.01	18.[illegible]	[illegible]	[illegible]	74.0	74.4	4.24	3.87	3.[illegible]	3.61	84	[illegible]
[illegible]																					
TH 6	Rest	18	13	4.79	4.[illegible]	0.78	0.78	173	190	20.64	20.[illegible]	[illegible]	[illegible]	73.3	[illegible]	3.18	3.[illegible]	3.[illegible]	3.[illegible]	[illegible]	73
40	Ex. I	16	16	[illegible]	10.[illegible]	0.78	0.73	455	[illegible]	21.[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	43.2	8.27	8.[illegible]	[illegible]	5.61	97	[illegible]
	Ex. II	20	21	16.13	15.40	0.81	0.73	730	877	[illegible]	20.41	97.1	97.0	43.3	44.4	10.77	10.84	7.02	[illegible]	113	123
1.65	Recy	15	18	4.77	5.19	0.78	0.74	173	200	20.77	19.[illegible]	[illegible]	97.0	[illegible]	[illegible]	[illegible]	[illegible]	3.13	2.22	74	74
[illegible]																					
GH 7	Rest	[illegible]	11	4.46	4.61	[illegible]	[illegible]	170	180	18.36	17.[illegible]	[illegible]	[illegible]	78.8	70.[illegible]	4.[illegible]	4.02	3.81	3.47	[illegible]	[illegible]
M, 33	Ex. I	23	21	14.81	14.[illegible]	[illegible]	0.84	444	878	19.63	17.62	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	7.06	120	120
1.[illegible]	Ex. II	27	30	19.63	17.41	[illegible]	0.82	727	677	19.80	18.47	[illegible]	[illegible]	[illegible]	40.3	[illegible]	[illegible]	7.48	7.42	140	131
1.87	Recy	19	13	6.18	5.30	[illegible]	[illegible]	161	136	18.43	17.62	[illegible]	[illegible]	78.1	[illegible]	5.01	4.87	3.62	2.78	87	[illegible]
[illegible]																					
GH 8	Rest	13	14	5.66	5.[illegible]	[illegible]	[illegible]	221	185	20.87	18.40	[illegible]	[illegible]	74.3	[illegible]	4.[illegible]	4.23	4.[illegible]	3.81	100	94
M, 45	Ex. I	15	16	10.30	10.31	[illegible]	[illegible]	421	444	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	63.7	6.87	7.96	6.13	5.87	120	104
1.83	Ex. II	20	17	15.19	13.82	[illegible]	[illegible]	[illegible]	677	21.66	19.80	[illegible]	[illegible]	[illegible]	46.2	[illegible]	[illegible]	[illegible]	[illegible]	120	111
1.73	Recy	13	13	4.82	4.37	[illegible]	[illegible]	183	188	20.67	19.34	97.2	96.7	74.9	73.3	4.43	4.23	4.08	3.[illegible]	105	[illegible]
78.5																					
GH 9	Rest	22	20	8.41	9.37	0.82	0.[illegible]	226	187	18.[illegible]	18.13	[illegible]	[illegible]	74.6	74.0	4.16	4.06	5.43	4.61	[illegible]	[illegible]
F, 36	Ex. I	23	41	13.99	17.13	[illegible]	0.91	479	430	18.[illegible]	19.[illegible]	[illegible]	94.4	[illegible]	[illegible]	7.06	7.01	6.18	[illegible]	100	100
1.74	Ex. II	23	23	16.78	19.18	[illegible]	0.82	[illegible]	880	19.61	19.24	[illegible]	94.8	[illegible]	47.5	9.41	9.30	[illegible]	[illegible]	116	112
1.[illegible]	Recy	21	24	10.06	12.06	[illegible]	0.81	188	190	19.12	18.[illegible]	[illegible]	[illegible]	71.4	72.3	4.[illegible]	4.46	4.00	4.25	[illegible]	[illegible]
72.1																					
GH 10	Rest	19	18	9.21	8.71	[illegible]	[illegible]	207	188	20.82	18.87	[illegible]	97.7	72.1	64.1	4.97	[illegible]	4.[illegible]	2.80	[illegible]	[illegible]
M, 33	Ex. I	19	23	13.61	19.90	[illegible]	0.78	412	419	[illegible]	19.22	97.3	[illegible]	[illegible]	[illegible]	9.13	8.41	5.28	4.[illegible]	112	[illegible]
1.[illegible]	Ex. II	25	28	27.00	21.36	1.00	[illegible]	736	830	[illegible]	19.33	97.2	[illegible]	46.1	47.0	10.67	9.22	[illegible]	[illegible]	140	110
1.[illegible]	Recy	18	18	7.41	10.42	[illegible]	0.93	171	171	19.90	18.23	[illegible]	[illegible]	71.[illegible]	62.9	3.37	[illegible]	3.13	3.73	[illegible]	[illegible]
63.[illegible]																					
GH 11	Rest	15	16	4.61	3.80	[illegible]	[illegible]	182	136	20.30	19.[illegible]	[illegible]	97.8	74.4	71.8	4.43	4.[illegible]	[illegible]	2.[illegible]	[illegible]	[illegible]
F, 45	Ex. I	17	17	8.31	[illegible]	[illegible]	[illegible]	300	324	[illegible]	[illegible]	[illegible]	[illegible]	44.4	[illegible]	7.18	7.16	4.61	4.62	122	100
1.71	Ex. II	18	17	13.63	13.[illegible]	[illegible]	0.91	522	483	[illegible]	19.[illegible]	[illegible]	94.3	46.1	[illegible]	9.14	9.16	[illegible]	[illegible]	141	120
1.67	Recy	18	18	4.41	4.12	[illegible]	[illegible]	147	112	20.63	18.78	[illegible]	97.9	75.[illegible]	73.6	4.75	4.56	3.27	2.[illegible]	[illegible]	[illegible]
64.[illegible]																					
GH 12	Rest	15	12	3.93	3.91	[illegible]	[illegible]	141	180	19.20	18.94	[illegible]	97.4	73.[illegible]	72.5	4.43	4.82	3.41	3.33	[illegible]	[illegible]
M, 20	Ex. I	15	18	8.62	9.40	[illegible]	[illegible]	303	321	19.65	19.62	[illegible]	[illegible]	[illegible]	[illegible]	7.87	[illegible]	[illegible]	4.87	120	112
1.70	Ex. II	19	18	12.04	11.74	[illegible]	[illegible]	622	622	[illegible]	18.[illegible]	[illegible]	[illegible]	44.3	41.4	[illegible]	8.25	6.23	[illegible]	123	122
1.71	Recy	11	13	4.24	4.67	0.[illegible]	[illegible]	113	112	19.64	19.21	[illegible]	[illegible]	74.0	73.[illegible]	4.[illegible]	4.41	2.22	3.31	[illegible]	87
61.[illegible]																					

hypertensive patients

Stroke volume (ml./sq. M.)		Vascular pressure (mm. Hg): Right atrial		Pulmonary arterial: Systolic		Pulmonary arterial: Diastolic		Pulmonary arterial: Mean		Pulmonary "wedge" (mean)		Aortic: Systolic		Aortic: Diastolic		Aortic: Mean		Vascular resistance (dynes sec. cm.$^{-5}$ sq. M.): Pulmonary		Vascular resistance: Systemic	
Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
44	49	7	—	26	28	21	19	24	20	14	14	232	174	130	85	149	129	208	107	1,187	2,347
80	65	—	—	64	61	41	27	43	30	30	21	270	192	135	81	189	171	179	109	2,991	2,193
62	70	—	—	48	44	27	17	31	28	18	10	206	157	115	86	178	136	153	211	2,879	1,970
81	25	—	7	22	23	15	19	20	16	12	11	210	165	104	85	143	110	183	243	2,456	4,153
43	41	6	—	26	30	15	14	17	18	9	9	196	151	108	73	143	93	190	144	3,885	1,967
80	81	—	—	45	34	28	19	31	34	12	9	250	148	171	84	188	111	284	227	2,318	1,748
60	57	—	—	30	31	39	24	25	21	12	6	275	190	147	86	184	120	182	184	1,884	1,443
40	20	—	6	27	22	17	12	13	13	6	6	172	130	104	64	122	102	155	136	3,090	2,210
25	45	5	—	31	28	15	12	18	14	16	6	182	148	108	62	143	118	167	121	3,349	2,325
44	33	—	—	30	29	23	20	24	27	13	13	222	175	112	102	147	135	194	132	2,784	1,718
33	33	—	—	43	43	31	31	27	25	12	13	223	171	114	98	201	137	150	124	2,021	1,474
40	41	—	5	25	27	15	20	17	18	9	11	196	140	112	94	143	117	169	138	3,306	2,894
43	49	6	—	23	24	12	20	22	22	13	13	170	143	100	86	131	123	213	229	3,123	2,138
47	57	—	—	44	44	30	33	21	23	21	19	204	181	114	79	184	150	146	176	2,230	1,780
63	66	—	—	47	51	25	41	32	34	28	20	208	189	104	93	148	132	149	188	1,690	1,333
42	44	—	6	31	29	30	25	21	23	30	11	190	146	69	87	123	115	212	274	3,227	2,180
42	37	6	—	24	23	18	16	19	12	11	8	213	173	110	108	167	127	180	93	3,250	2,186
49	57	—	—	40	32	29	17	31	21	13	14	278	221	153	122	208	171	189	80	2,789	1,827
51	57	—	—	49	34	28	30	30	19	17	14	273	223	148	109	209	190	120	83	2,811	1,695
37	36	—	5	26	19	14	11	16	11	11	8	195	154	115	96	182	119	110	68	3,363	2,479
43	43	6	—	14	24	19	16	20	16	11	10	277	140	130	90	166	115	146	135	2,720	2,414
40	33	—	—	34	46	24	27	29	23	18	22	236	172	121	95	190	122	92	142	2,206	1,807
40	35	—	—	22	48	24	27	24	23	17	19	291	170	136	82	173	136	84	170	2,084	1,861
30	44	—	6	22	23	18	18	17	17	8	10	301	140	130	91	186	119	176	113	3,099	2,377
30	49	3	—	25	27	14	17	16	19	8	10	244	200	122	117	178	147	163	127	2,019	2,733
38	39	—	—	32	41	20	22	21	26	10	11	273	241	141	120	202	169	144	100	2,615	2,233
30	57	—	—	29	29	30	21	22	31	11	9	209	220	130	111	187	144	185	190	2,225	1,971
44	45	—	3	27	19	13	19	16	17	7	9	240	200	122	118	155	141	178	130	3,333	2,735
48	38	5	—	33	32	17	18	23	18	19	9	241	183	140	113	182	130	290	300	3,610	4,778
47	30	—	—	66	46	38	33	44	29	21	15	313	231	174	127	230	174	303	233	3,671	2,006
47	42	—	—	30	45	30	33	30	30	27	14	231	227	148	126	202	174	300	159	2,921	2,418
33	35	—	5	38	24	20	12	22	14	10	8	330	142	141	108	151	130	300	173	4,335	3,871
36	33	5	—	32	30	19	19	20	19	10	11	250	208	140	121	270	188	234	314	4,918	4,334
40	43	—	—	48	46	28	37	34	33	21	15	309	235	148	134	250	173	212	341	2,714	3,005
42	42	—	—	49	43	25	20	32	31	19	15	302	204	137	130	237	180	187	187	2,117	2,871
34	33	—	5	30	30	18	19	19	18	9	10	303	198	148	118	187	132	344	221	4,817	4,178
36	37	4	—	34	29	18	18	20	18	8	8	240	193	130	100	190	145	238	183	4,333	3,000
43	44	—	—	43	40	30	24	22	30	17	16	280	212	113	113	190	137	240	234	3,000	2,806
49	32	—	—	33	61	21	27	30	31	12	13	254	218	142	113	195	148	230	238	2,431	1,967
38	37	—	4	31	30	18	18	17	18	7	8	230	167	130	104	178	140	249	190	4,994	3,403

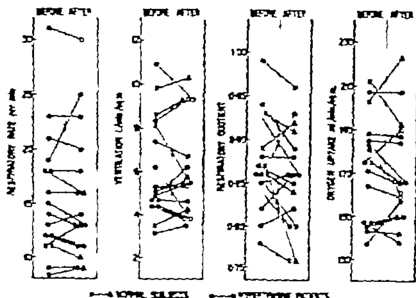


Fig. 2. Effects of intravenous guanethidine on the respiratory rate, ventilation, respiratory quotient, and oxygen uptake of 4 normal subjects and 12 hypertensive patients at rest in the supine position. Observations before and after the drug.

either the normal subjects or the hypertensive patients at either of the two levels of exercise.

Although there was some individual variation, there was no discernible trend in the resting ventilatory minute volume of either normal subjects or hypertensive patients after intravenous injection of the drug. The average values of minute ventilation for both groups before and after the drug were not significantly different (Table II). The response of the ventilatory minute volume to similar levels of exercise and oxygen uptake was largely unchanged by guanethidine both in the 4 normal subjects and in the 12 hypertensive patients.

Oxygen uptake and respiratory quotient. The individual values of the resting oxygen uptake before and after intravenous guanethidine in the normal and hypertensive subjects are shown in Fig. 2. Although the oxygen uptake was increased in 1 normal subject and 2 of the hypertensive patients after the injection of the drug, decreases of the same order were observed in a similar number of subjects; in the remainder there was no appreciable change. The average resting oxygen uptakes of the 4 normal subjects before and after injection of the drug were 155 ml./min./sq.M. (S.D. = 30) and 153 ml./min./sq.M. (S.D. = 32) respectively. The corresponding values for the 12 hypertensive patients were 169 ml./min./sq.M. (S.D. = 22) and 167 ml./min./sq.M. (S.D. = 21) respectively. During similar levels of supine leg exercise before and after the injection of the drug there was some variation in the oxygen uptake in individual instances at each level, but the average oxygen uptakes of both groups of subjects at each level of exercise were very similar (Table II).

Although the resting respiratory quotient (RQ) showed individual variation before and after the injection of guanethidine, these changes were small and there was no discernible trend. In the 4 normal subjects the average RQ at rest was 0.89 (S.D. = 0.031) before and 0.86 (S.D. = 0.023) after the drug. The corresponding average values in the 12 hypertensive patients were 0.87 (S.D. = 0.019) and 0.86 (S.D. = 0.018) respectively. The maximum increase in the RQ during exercise either before or after the drug in the normal and hypertensive subjects was 0.11 (Patient GH 7); in all the other patients the increase in the RQ during exercise was less than this.

Arterial blood oxygen saturation and arteriovenous blood oxygen content difference. The average resting arterial oxygen satura-

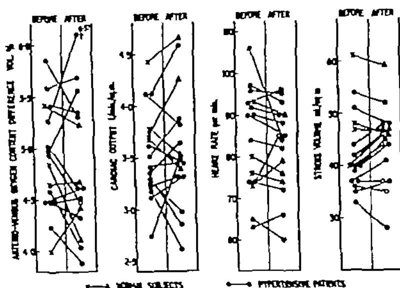


Fig. 3. Effects of intravenous guanethidine on the A-V difference, cardiac output, heart rate, and stroke volume of 4 normal subjects and 12 hypertensive patients at rest in the supine position. Observations before and after the drug.

tion of the normal subjects was 97.9 per cent (S.D. = 0.83) before and 97.7 per cent (S.D. = 0.77) after the drug. The corresponding values for the hypertensive patients were 96.6 per cent (S.D. = 1.37) and 96.5 per cent (S.D. = 0.99) respectively. Exercise was not associated with a significant reduction in arterial blood oxygen saturation either before or after the drug in either the normal subjects or hypertensive patients.

The individual values of the resting arteriovenous blood oxygen content difference (A-V diff.) before and after the drug are illustrated in Fig. 3. Although there were some considerable variations in the individual resting values, there was no consistent trend after the drug in either group of subjects (Table II).

Cardiac output. The individual values of the resting cardiac output before and after guanethidine in both the normal subjects and hypertensive patients are given in Table I and illustrated in Fig. 3. One of the normal subjects and 4 of the hypertensive patients showed small reductions (of 0.25 to 0.54 L./min./sq.M.) and 1 of the normal and 4 of the hypertensive subjects showed small increases (of 0.25 to 0.76 L./min./sq.M.) but the other 2 normal and 4 hypertensive subjects showed no appreciable change in the resting cardiac output after the drug. The average resting cardiac outputs of the 4 normal subjects before and after injection of the drug were 3.90 L./min./sq.M. (S.D. = 0.355) and 3.9[illegible] L./min./sq.M. (S.D. = 0.601) respectively; the corresponding average cardiac outputs of the hypertensive group were 3.41 L./min./sq.M. (S.D. = 0.384) and 3.46 L./min./sq.M. (S.D. = 0.524) respectively.

The cardiac output response during the two levels of supine leg exercise before and after guanethidine is shown in each individual in Fig. 4. Prior to injection of the drug the response was normal at both levels of exercise in all the subjects studied. After guanethidine the exercise response of the cardiac output was largely unchanged in all individuals, and no significant trend was detectable between the average values of the cardiac output at both levels of exercise in either group of subjects. The average values at rest and at each level of exercise for each group are given in Table II and illustrated graphically in Fig. 5. It will be seen, therefore, that administration of the drug intravenously in a dose sufficient to cause a substantial lowering of the resting blood pressure in the supine position had no appreciable effect on the resting cardiac

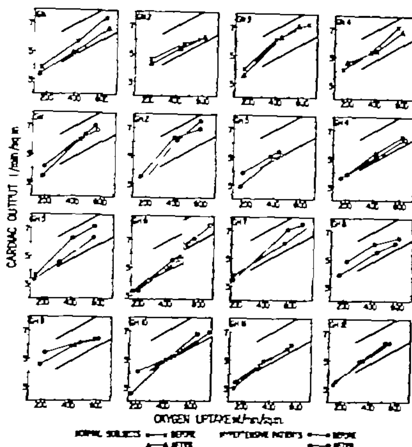


Fig. 4. Individual observations on the cardiac output, at rest and during graded leg exercise, in 4 normal subjects and 12 hypertensive patients before and after guanethidine. In each patient the cardiac output is related to oxygen uptake, and the 95 per cent confidence limits for 16 other normal subjects during supine leg exercise are shown in each case. For the sake of clarity the recovery values are omitted in all instances.

output or on the cardiac output response to exercise in any individual or in either group of subjects as a whole.

Heart rate and stroke volume. The effects of the drug on the resting heart rate and stroke volume of each subject are shown in Fig. 3. Marked changes in the resting heart rate were observed in only 2 hypertensive patients, the changes being in opposite directions; there was no significant trend in the resting heart rate after the drug in either group of subjects (Table II). The average resting heart rates of the 4 normal subjects before and after guanethidine were 81 per minute (S.D. = 8.8) and 80 per minute (S.D. = 7.1) respectively; the corresponding values for the 12 hypertensive patients were 85 per minute (S.D. = 13.5) and 83 per minute (S.D. = 11.4), respectively.

The response of the heart rate to supine leg exercise was modified by the drug, as shown in Fig. 6. Although ventilation, oxygen uptake, and cardiac output during exercise were all unchanged by the drug and although there was no change in the resting heart rates after the drug, the heart rates during exercise after the drug were less at a given oxygen uptake and cardiac output in both groups of subjects than the values recorded before the drug was injected. Before the drug was given, the average heart rates during light and moderate exercise in the 4 normal subjects were 101 beats per minute (S.D. = 16.1) and 117 beats per minute (S.D. = 14.2), respectively. After the drug, at nearly identical levels of work, oxygen uptake, and cardiac output, the average heart rates were 90 beats per minute (S.D. = 7.3) and

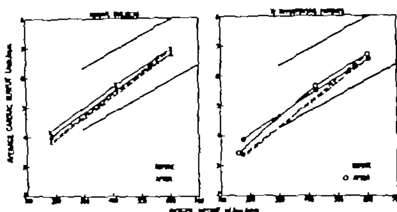


Fig. 5. The average cardiac output at rest, during graded supine leg exercise and during recovery related to the average oxygen uptake in 4 normal subjects and 12 hypertensive patients before and after guanethidine. The 95 per cent confidence limits for 16 other normal subjects during supine leg exercise are also illustrated. The broken line represents the return to the recovery value.

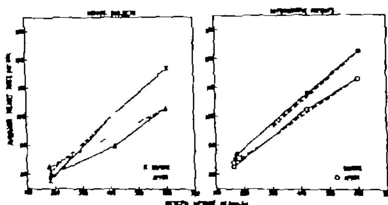


Fig. 6. The average heart rate at rest, during graded supine leg exercise, and during recovery related to the average oxygen uptake in 4 normal subjects and 12 hypertensive patients before and after guanethidine. The broken line represents the return to the recovery value.

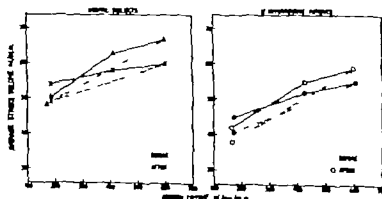


Fig. 7. The average stroke volume at rest, during graded supine leg exercise, and during recovery related to the average oxygen uptake in 4 normal subjects and 12 hypertensive patients before and after guanethidine. The broken line represents the return to the recovery value.

Table III The dose response relationship of the resting systemic blood pressure and vascular resistance and guanethidine dose

Patient	Weight (Kg)	Reduction		Guanethidine	
		Mean aortic pressure (mm. Hg)	Systemic vascular resistance (dynes sec cm⁻⁴ sq M)	mg	mg/Kg
GN 1	69 3	16	199	29	0 419
GN 2	74 2	5	351	25	0 337
GN 3	70 3	20	327	33	0 469
GN 4	59 4	26	550	40	0 673
GH 1	62 5	17	452	17	0 272
GH 2	80 0	8	1 000	15	0 188
GH 3	89 0	23	118	20	0 225
GH 4	58 3	38	1 052	15	0 257
GH 5	56 0	28	880	18	0 321
GH 6	60 5	16	592	10	0 165
GH 7	66 0	15	199	15	0 227
GH 8	70 5	43	675	25	0 355
GH 9	72 1	25	832	10	0 139
GH 10	63 0	45	357	20	0 317
GH 11	64 0	39	583	18	0 281
GH 12	61 0	24	699	15	0 216

103 beats per minute (S D = 9 9) respectively in these same subjects. Similar changes were observed in the 12 hypertensive patients Before the drug the average heart rates during light and moderate exercise in these patients were 103 beats per minute (S D = 15 4) and 123 beats per minute (S.D = 19 7) respectively After the drug the corresponding average values were 103 beats per minute (S.D = 15 4) and 113 beats per minute (S.D = 17 1) respectively

The individual values of the resting stroke volume before and after intravenous guanethidine are illustrated in Fig 3 Although there were small individual changes in stroke volume after injection of the drug there was no significant effect of the drug on the average resting stroke indices of either group of subjects as a whole (Table II) The average resting stroke index of the 4 normal subjects was 49 ml sq M (S D = 8.8) before and 50 ml /sq.M (S D = 6.2) after the drug The corresponding values for the 12 hypertensive patients were 41 ml./sq M (S D = 6.3) and 42 ml./sq M (S D = 6 7) respectively As would be expected from the unchanged cardiac output and reduced heart rate during exercise that occur after the drug the average stroke volumes of both the normal subjects and the hypertensive patients show a small but definite increase at both levels of exercise after the drug (Fig 7)

Systemic arterial blood pressure The *immediate effects of the intravenous ad*ministration of guanethidine at a dose rate of 1 to 2 mg per minute were slight None of the patients experienced any subjective sensations and the injection of the drug at this rate had no immediate effect on the systemic blood pressure. Aortic blood pressure was recorded constantly throughout but no immediate hypotensive or hypertensive phase was detected in any of these subjects In all cases the blood pressure started to fall within 2 to 10 minutes of commencement of the intravenous injection of the drug and the reduction in pressure was steady slow and predictable and unaccompanied by any subjective sensations.

The second period of observation was begun 30 to 60 minutes after completion of the injection of guanethidine at which time the Valsalva maneuver showed unequivocal evidence of complete sympathetic blockade At this time the resting aortic blood pressure was reduced in all

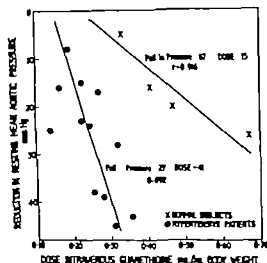


Fig. 8 The dose-response relationship between intravenous guanethidine and the reduction in mean aortic blood pressure in 4 normal subjects and 12 hypertensive patients. The equations which represent the lines of correlation, together with the correlation coefficients, are also given

subjects, and the reduction in the mean arterial pressure correlated well with the dose of the drug given (Table III) The normal subjects exhibited a much smaller fall in blood pressure for a given dose of guanethidine than did the hypertensive patients. In fact the highest dose of the drug given to a hypertensive patient (0.355 mg /kg of body weight) was associated with a fall of 43 mm. Hg in the mean aortic pressure a similar dose of guanethidine (0.337 mg /kg of body weight) caused a fall of only 5 mm. Hg in the mean aortic pressure of a normal subject This difference in the sensitivity of the response of blood pressure to the hypotensive effects of the drug in the two groups is well illustrated in Fig 8. In the 4 normal subjects the intravenous administration of the drug in an average dose of 0 475 mg /kg of body weight (range 0 337-0 673) was associated with an average reduction in the systolic diastolic, and mean aortic pressures of 20 mm Hg (range 4-38) 13 mm Hg (range 4-19) and 17 mm Hg (range 5-26) respectively In the 12 hypertensive patients the average dose of guanethidine was 0.249 mg./kg of body weight (range 0 139-0.355) and was associated with average falls in systolic, diastolic and mean aortic pressures of 38 mm Hg (range 8-77) 19 mm. Hg (range 8-29) and 27 mm. Hg (range 8-45) Furthermore, in the hypertensive patients the magnitude of the reduction in arterial pressure after a given dose of drug did not appear to be related to either the initial level of mean or systolic blood pressure

In the 4 normal subjects the mean resting aortic pressure was 104 mm Hg (S D = 7 7) before, and 87 mm Hg (S D = 7 9) after guanethidine The corresponding values for the 12 hypertensive patients were 156 mm. Hg (S D = 22 6) before and 129 mm Hg (S.D = 19.3) after administration of the drug (Fig 9)

The response of the blood pressure to exercise was considerably modified by the drug The individual responses of the pulsatile blood pressure to supine leg exercise before and after the drug are shown in Fig 10 Before administration of the drug such exercise was associated with an increase in both the systolic and diastolic pressures particularly during the period of light exercise this increase was most marked in the hypertensive patients. In the majority of the normal subjects and hypertensive patients the additional period of heavier exercise was associated with little change in the aortic blood pressure although in a few instances there was

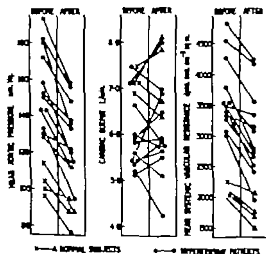


Fig 9 Effects of intravenous guanethidine on the mean aortic blood pressure cardiac output, and mean systemic vascular resistance of 4 normal subjects and 12 hypertensive patients at rest in the supine position. Observations before and after the drug

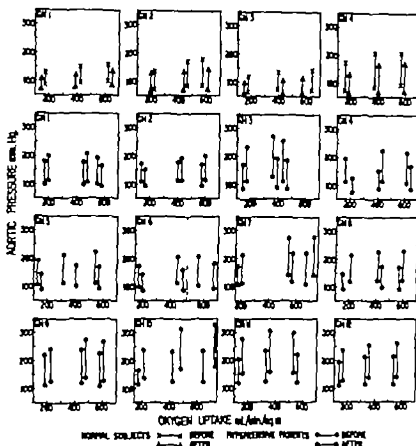


Fig. 10 Individual observations on the systolic and diastolic systemic blood pressure, at rest and during graded leg exercise, in the supine position in 4 normal subjects and 12 hypertensive patients before and after guanethidine. The blood pressure is related to oxygen uptake in each instance and for the sake of clarity the initial resting and final recovery values are omitted (see Result in text).

either a small increase or small reduction in pressure from that obtaining during the period of light exercise. After intravenous injection of the drug the resting systemic arterial blood pressure was reduced in all subjects (*vide supra*). However exercise was still associated with an increase in aortic blood pressure above the resting value and again the increase was usually most marked in the period of light exercise. Thus although the resting systemic blood pressure was reduced by intravenous guanethidine the response of the blood pressure to exercise followed closely the pattern seen before injection of the drug.

The average mean aortic blood pressure of both normal and hypertensive subjects at rest and during exercise before and after the injection of guanethidine is shown in Fig. 11. This demonstrates graphically that the pattern of response of the blood pressure to supine leg exercise in both normal subjects and hypertensive patients is unchanged although lower at all times after the drug.

In no instance during or after the supine leg exercise was any abrupt fall in the systemic arterial pressure below the initial resting level seen. It is of interest to note that in all subjects, both normal and hypertensive, the systemic blood pressure remained considerably depressed after the injection for at least 8 hours, and in some of the hypertensive patients for as much as 16 hours after the single intravenous injection of the dose of guanethidine stated in Table III. During this time the blood pressure as recorded by sphygmomanometer remained relatively stable at the

level obtaining shortly after the intravenous injection of the drug there was a marked postural effect throughout this time. These antihypertensive effects had largely or completely disappeared in both normal and hypertensive subjects after 24 hours.

Systemic vascular resistance The determinations of the individual resting systemic vascular resistance before and after intravenous guanethidine are given in Table I and illustrated in Fig 9 After the intravenous injection of the drug a reduction in the resting systemic vascular resistance was observed in all 4 normal subjects and in all 12 hypertensive patients. The dose-response relationship was similar to that observed between the intravenous dose of guanethidine and the reduction in mean aortic blood pressure the fall in the mean systemic vascular resistance after the drug was directly proportional to the dose administered in both groups of subjects (Table III) However the absolute fall in the mean systemic vascular resistance of the normal subjects was much less for a given dose of drug than that of the hypertensive patients, a relationship analogous to that observed between the dose of guanethidine and the reduction in arterial pressure Thus although there was a good positive correlation between the dose of drug and the fall in systemic vascular resistance in both the normal subjects and the hypertensive patients the equations representing the regression lines were again significantly different.

In the 4 normal subjects the intravenous injection of guanethidine caused an average fall in the mean resting systemic vascular resistance of 357 dynes sec. cm $^{-5}$ sq M (from 2 125 to 1 768 range of fall in individual subjects 199-550) In the 12 hypertensive patients the average fall in the mean systemic vascular resistance was 620 dynes sec. cm.$^{-5}$ sq M (from 3 673 to 3,053 range of fall in individual patients 188-1,052) In both groups the reduction in the average mean resting systemic vascular resistance after the drug was 17 per cent, although the average dose of drug in the normal subjects was *nearly* double that in the hypertensive patients. In both groups this fall in the resting systemic vascular resistance was statistically significant (0 05 > p > 0 02) The pattern of the response to exercise of the mean systemic vascular resistance was largely unchanged by the drug in either group of subjects in spite of the fall in the resting values after the drug (Fig 12) Before the drug consecutive light and moderate exercise were associated with average reductions of 18 and 30 per cent, respectively in the mean systemic vascular resistance from the resting values in the 4 normal subjects and 22 and 35 per cent respectively in the 12 hypertensive patients After intravenous injection of guanethidine the average mean systemic vascular resistances were reduced in both groups. Levels of exercise similar to those performed before the drug was given were now associated with reductions in the average mean systemic vascular resistance of 22 and 34 per cent respectively in the normal subjects and 31 and 44 per cent respectively in the hypertensive patients. It is apparent, therefore that the drug was responsible for only a 4 per cent greater fall in the average mean systemic vascular resistance of the normal subjects during both levels of exercise than during the control study In the hypertensive patients a much smaller dose of drug was responsible for an additional fall of 9 per cent in the average mean systemic vascular resistance at both levels of exercise over that observed during the control study

Interrelationship of cardiac output, blood pressure and systemic vascular resistance The relative contribution of cardiac output and mean systemic vascular resistance to the mean systemic arterial blood pressure in normal subjects and hypertensive patients at rest and during moderate exercise is shown in Fig 13

At rest the predominant trend in all subjects was for the drug to reduce the blood pressure chiefly by reduction of the mean systemic vascular resistance this was particularly noticeable in the hypertensive subjects. The same trend was noted during moderate exercise in both groups in spite of the increased scatter of the observations

Pulmonary wedged pressure The resting mean pulmonary wedged pressure was less than 12 mm. Hg in all the normal subjects and hypertensive patients before administration of the drug In the 4 no

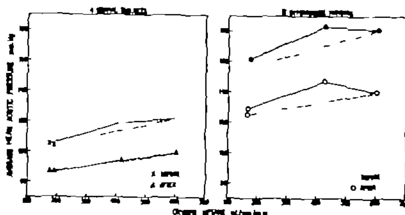


Fig. 11. The average mean aortic blood pressure at rest, during graded supine leg exercise, and during recovery related to the average oxygen uptake in 4 normal subjects and 12 hypertensive patients before and after guanethidine. The broken line represents the return to the recovery value.

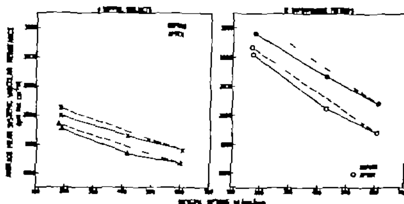


Fig. 12. The average mean systemic vascular resistance at rest, during graded supine leg exercise, and during recovery related to the average oxygen uptake in 4 normal subjects and 12 hypertensive patients before and after guanethidine. The broken line represents the return to the recovery value.

jects the average mean pulmonary wedged pressure was 9 mm. Hg (S.D. = 1.3, total range 8-11) and in the 12 hypertensive patients the average mean resting wedged pressure was 9 mm. Hg (S.D. = 1.7, total range 7-12). After intravenous injection of guanethidine there were no important changes in the pulmonary wedged pressure (Fig. 14). The average mean resting pulmonary wedged pressure of the normal subjects was unchanged at 9 mm. Hg (S.D. = 1.2, total range 8-10) and the average mean resting pulmonary wedged pressure of the hypertensive patients was 10 mm. Hg (S.D. = 2.1, total range 7-14).

Before the drug both levels of exercise were associated with an increase in the pulmonary wedged pressure of all subjects. In the 4 normal subjects and 12 hypertensive patients the average mean pulmonary wedged pressure increased during light exercise to 18 mm. Hg (S.D. = 1.0, total range 17-19) and 18 mm. Hg (S.D. = 5.5, total range 10-30), respectively. An additional consecutive 6-minute period of heavier exercise was associated with a small reduction in the mean pulmonary wedged pressure in all the normal subjects and in all but one (Patient GH 9) of the hypertensive patients. During this heavier exercise in these two groups of subjects the average mean pulmonary wedged pressure was 15 mm. Hg (S.D. = 0.6, total range 14-15) and 16 mm. Hg (S.D. = 3.7, total range 11-12), respectively. After intravenous injection of the drug, exercise was

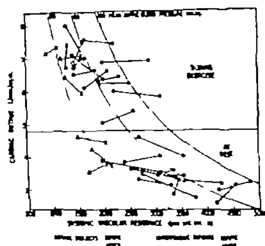


Fig. 13. The relative contributions of cardiac output and systemic vascular resistance to the mean aortic pressure at rest and during moderate exercise in 4 normal subjects and 12 hypertensive patients before and after intravenous guanethidine. The only important change affecting the blood pressure is that of the systemic vascular resistance. Before and after guanethidine the degree of exercise and oxygen uptake were repeated as closely as possible, but some variation was inevitable.

associated with similar but somewhat smaller increases in the mean pulmonary wedged pressure. From average resting levels of 9 mm. Hg (S.D. = 1.2, total range 8-10) in the normal group and 10 mm. Hg (S.D. = 2.1, total range 7-14) in the hypertensive group there was an increase during light exercise to 13 mm. Hg (S.D. = 0.8, total range 12-14) and 16 mm. Hg (S.D. = 4.2, total range 9-22) respectively, a smaller increase than before the drug. As during the control study, an additional period of continuous but heavier exercise was again associated with a small reduction in the pulmonary wedged pressure in all except one normal subject (Patient GN 1) and 3 hypertensive patients (Patients GH 4, 6, and 7). The average mean pulmonary wedged pressure during moderate exercise after the drug was 13 mm. Hg (S.D. = 1.7, total range 12-15) for the group of 4 normal subjects and 14 mm. Hg (S.D. = 4.0, total range 8-20) for the group of 12 hypertensive patients.

Pulmonary arterial pressure. The average resting mean pulmonary arterial pressure of the normal subjects and hypertensive patients before the drug was given was 16 mm. Hg (S.D. = 1.3, total range 15-17) and 19 mm. Hg (S.D. = 2.2, total range 16-22) respectively. During light exercise this increased to an average value of 24 mm. Hg (S.D. = 0) and 32 mm. Hg (S.D. = 7.5, total range 21-44) respectively. During further continuous but heavier exercise the mean pulmonary arterial pressure decreased in all normal subjects and in all but 3 (Patients GH 5, 6, and 9) of the hypertensive patients. The average values of the pulmonary arterial pressure during moderate exercise before the drug were 22 mm. Hg (S.D. = 1.5, total range 20-23) and 30 mm. Hg (S.D. = 5.4, total range 22-39) respectively.

After intravenous injection of the drug there was a small reduction in the resting pulmonary arterial pressure in 3 of the 4 normal subjects and in 7 of the 12 hypertensive patients (Fig. 14). The average resting mean pulmonary arterial pressures after the drug were 14 mm. Hg (S.D. = 1.7, total range 12-16) in the normal subjects and 18 mm. Hg (S.D. = 3.3, total range 13-23) in the hypertensive patients as compared with average resting values of 16 and 19 mm. Hg respectively in the two groups before the drug. During light exercise after the drug the average mean pulmonary arterial pressure increased to a mean of 21 mm. Hg (S.D. = 2.1, total range 13-24) in the

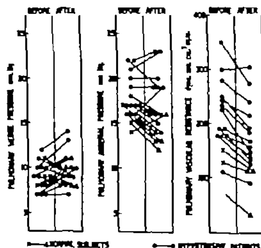


Fig. 14. Effects of intravenous guanethidine on the pulmonary wedged and arterial pressures and the mean pulmonary vascular resistance in 4 normal subjects and 12 hypertensive patients at rest in the supine position. Observations before and after the drug.

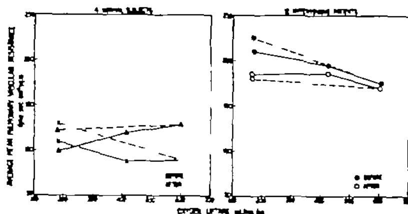


Fig. 15. The average mean pulmonary vascular resistance at rest, during graded supine leg exercise, and during recovery related to the average oxygen uptake in 4 normal subjects and 12 hypertensive patients before and after guanethidine. The broken line represents the return to the recovery value.

normal subjects and 29 mm. Hg (S.D. = 4.5, total range 21-36) in the hypertensive patients. During further continuous but heavier exercise the average mean pulmonary arterial pressure increased in all the normal subjects (mean 24 mm. Hg, S.D. = 1.5, total range 22-25) and in 4 of the 12 hypertensive patients (mean 23 mm. Hg, S.D. = 4.8, total range 19-32).

Pulmonary vascular resistance. The individual values of the resting mean pulmonary vascular resistance before and after the intravenous injection of guanethidine are given in Table I and illustrated in Fig. 14. Administration of the drug was followed by a small reduction in the resting mean pulmonary vascular resistance in all the normal subjects and in all but one (Patient CH 10) of the hypertensive patients. In the 4 normal subjects the average mean pulmonary vascular resistance was 131 dynes sec. cm.$^{-5}$ sq. M. (S.D. = 43.6) before and 100 dynes sec. cm.$^{-5}$ sq. M. (S.D. = 46.0) after the drug, a reduction of 24 per cent ($p > 0.05$). In the 12 hypertensive patients the average resting values were 22[illegible] dynes sec. cm.$^{-5}$ sq. M. (S.D. = 64.3) before and 186 dynes sec. cm.$^{-5}$ sq. M. (S.D. = 63.3) after the drug, a reduction of 18 per cent ($p > 0.05$). Thus, although the drug causes a small but consistent reduction in the resting pulmonary vascular resistance in both normal subjects and hypertensive patients, this reduction does not achieve statistical significance for the groups as a whole because of the scatter of the observations and the small number of subjects used. The pattern of the response to exercise of the mean pulmonary vascular resistance also appears to be modified by the drug in both normal subjects and hypertensive patients (Fig. 15). In the normal subjects during the control study light exercise for 6 minutes was accompanied by a reduction of 20 per cent in the average mean pulmonary vascular resistance. An additional 6 minutes of consecutive but heavier exercise was not associated with any further reduction in the mean pulmonary vascular resistance; the average was 17 per cent below the resting value. After the drug, although there was a reduction in the resting mean pulmonary vascular resistance, light exercise was now associated with an increase of 19 per cent in this resistance and a further period of heavier exercise was associated with an increase of 28 per cent above the resting level. In the hypertensive patients, light and moderate exercise before the drug was associated with reductions in the average mean pulmonary vascular resistance of 8 and 18 per cent, respectively. After the drug, although there was a fall of 18 per cent in the resting average pulmonary vascular resistance, light exercise was now associated with an increase of 1 per cent compared to a fall of 8 per cent beforehand and the moderate exercise was now associated with a fall in resistance of 10 per cent, as compared to a fall of 18 per cent in the control study.

Blood volume. The total circulating blood volume was determined during the initial resting period and during recovery both before and after the drug in 2 hypertensive patients (Patients GH 6 and GH 8). In neither patient was there any appreciable change in blood volume throughout the course of the investigation (Table IV). Since the hemodynamic changes which resulted from the administration of the drug in these 2 patients were similar in all respects to those observed in the other subjects studied, it is reasonable to assume that changes in plasma volume are not an important factor in the immediate circulatory effects of the intravenously injected drug.

Discussion

The observations reported in the present paper confirm and extend those in an earlier preliminary report on the circulatory effects of intravenous guanethidine in 5 hypertensive patients.[1]

There are a number of interesting points in regard to the immediate effects of the drug on the systemic blood pressure. Although the aortic blood pressure was continuously recorded before, during, and for up to 2 hours after the intravenous injection of guanethidine, no "hypertensive" phase was observed at any time in any subject. In addition, the intravenous injection of the drug at 1 to 2 mg. per minute was never associated with any abrupt fall in the systemic blood pressure. It is possible that this relatively slow rate of injection of the drug may account for these findings, although even with more rapid intravenous injections (5 mg. injected during 1 minute) no transient "hypotensive" or "hypertensive" phase has been seen. These effects contrast markedly with those of bretylium tosylate injected intravenously in normal and hypertensive subjects at a comparable rate.[3] In many previous reports of transient elevation of the blood pressure in hypertensive patients after the intravenous injection of guanethidine the exact rate of injection has not been given, and continuous intra-arterial blood pressure records were usually not taken. Page and Dustan,[1] in their original report on the drug, observed that the intravenous administration of guanethidine to anesthetized dogs caused an abrupt fall in systemic blood pressure, followed by a marked pressor response that lasted for an hour or more. However, they were using very high intravenous doses ranging from 10 to 15 mg. per kilogram of body weight, more than 40 times the dose used in the present studies. It appears, therefore, that if the drug is injected at a rate of 1 to 2 mg. per minute in normal subjects or patients with uncomplicated hypertensive disease, no subjective side effects or adverse abrupt hypotensive or hypertensive reactions are likely to be encountered.

The characteristics of the fall in systemic blood pressure which follows the intravenous injection of guanethidine differ in certain important respects from those which follow the administration of other antihypertensive drugs. The reduction in systemic arterial pressure after guanethidine was not accompanied by the abnormal reduction in pulse pressure which usually follows the intravenous injection of hexamethonium and similar ganglion blocking drugs. This is almost certainly due to the fact that the latter drugs achieve

Table IV. Effect of guanethidine on the blood volume

Patient	Blood volume (ml.)			
	Before		After	
	Rest	Recovery	Rest	Recovery
GH 6	6 390	6,310	6 120	6 220
GH 8	4 970	4 930	4 [illegible]40	5 000

much of their effects on the blood pressure by reduction of the cardiac output and stroke volume whereas these parameters are largely unchanged after intravenous guanethidine Furthermore there was no sudden marked fall in diastolic or mean blood pressure either during or after supine leg exercise, as was seen in some hypertensive patients after the injection of bretylium [1]

Even in the relatively short time-course of the present investigation there was a striking correlation between the dose of the drug injected and the final resultant fall in the resting systemic arterial blood pressure Since the cardiac output was unchanged the fall in systemic blood pressure was due to a consistent and quantitative reduction in the total systemic vascular resistance in both the normal subjects and the hypertensive patients. Furthermore the appreciable difference in degree of effect of the drug on the arterial pressure of the two groups is of considerable interest Although the majority of previous reports based largely on measurements of blood flow in the skin have disclaimed any increased sympathetic tone in uncomplicated hypertensive disease the present findings appear to suggest such an increase in sympathetic activity in this disease Brod[4] has adduced evidence albeit incomplete that the patient with essential hypertension even at rest is in a state similar to that of a normal person who is under mental or physical stress and he considers that it is likely that the hypertensive patient is in a state of chronic sympathetic overactivity If such a state of sympathetic overactivity exists in hypertensive patients, as Brod suggests then it would be expected that sympathetic-blocking drugs, such as guanethidine would cause a greater fall in the systemic vascular resistance of such patients than of normal subjects. Although the results of the present study give some support to this hypothesis, such a fundamentally important concept needs considerably more direct evidence than that of the single pharmacologic experiment reported here

The effects of guanethidine on the cardiac output are of considerable importance and contrast sharply with the effects of the ganglion-blocking drugs such as hexamethonium or pentolinium which achieve much of their antihypertensive effect by reducing the cardiac output In the doses used guanethidine had no effect on the resting cardiac output or on the response of the cardiac output to leg exercise in normal or hypertensive subjects in the supine position In this respect the drug resembles the other sympathetic blocking drug bretylium tosylate except that the latter drug was found to cause a small but statistically significant increase in the resting cardiac output [1]

The total circulatory effect of guanethidine appears to bring the hypertensive patient nearer to a normal systemic vascular behavior than do any of the other ganglion blocking or sympathetic blocking drugs so far studied At present our general impression is that the acute systemic circulatory effects of intravenous guanethidine are largely those related to its sympathetic blocking action. The circulatory effects of the chronic administration of the drug appear to be a combination both of its sympatholytic and reserpine-like activities. In fact the circulatory findings after oral guanethidine are very similar to those observed in hypertensive patients after the prolonged oral administration of reserpine (Taylor Reeves and Donald report in preparation)

The factors responsible for the exercise hypotension observed in some hypertensive patients who are taking oral guanethidine remain to be clarified To the best of our knowledge exercise hypotension after the intravenous injection of the drug has not been described In the present study it has been demonstrated that the pattern of response of the blood pressure to exercise is unchanged by the intravenous route of administration in both normal and hypertensive subjects, in spite of the appreciable falls in the resting blood pressure which occurred after injection of the drug However all the hypertensive patients investigated in the present series were fit and leading normal active lives and were without any clinical or laboratory evidence of cardiac insufficiency Although hypotension during supine leg exercise after the oral administration of guanethidine has been reported in individual cases by a number of observers, in all instances no control ob-

servations were carried out before treatment. We have never observed the systemic arterial blood pressure to fall appreciably below resting levels during supine leg exercise or even during treadmill walking in patients with uncomplicated hypertensive disease (many of whom took part in the present investigation) either before or during oral therapy with guanethidine (report in preparation). In this respect it is of considerable interest that Vernikos-Danellis and Zaimis[6] have recently postulated that myocardial contractility may be depressed by the drug and they have shown that such effects are particularly apparent in animals with myocardial damage. Previous reports of exercise hypotension after oral guanethidine have not always defined with precision the clinical state of the patients under study, but the majority were apparently elderly and had severe hypertensive disease, conditions known to be associated with a very high incidence of coronary arterial disease and incipient myocardial insufficiency. Such patients, if treated energetically with guanethidine, would be much more likely to develop arterial "hypotension" during exercise even in the supine position if they already suffer from left ventricular insufficiency with impairment of the response of cardiac output during exercise. Although this subject needs more careful study, the clinical importance of Zaimis' findings, if confirmed, is obvious.

Both guanethidine and bretylium suppress compensatory vasoconstriction and "overshoot" during and after the Valsalva maneuver, respectively, but there are certain differences in the effect of these sympathetic blocking drugs on the regional circulatory behavior during supine leg exercise. These are being reported in detail in a second paper. However, it may be briefly mentioned that, whereas bretylium causes a very considerable reduction in the vasoconstriction that normally occurs in nonexercising muscles during supine leg exercise,[1,4] this reduction is far less in the case of guanethidine. This may well account for the absence of systemic arterial hypotension during supine exercise after the intravenous injection of guanethidine.

Another important difference between the two drugs is seen in their effects on the pulmonary circulation. Whereas bretylium has been shown to cause an increase in the pulmonary vascular resistance in both normal and hypertensive subjects, guanethidine causes a small reduction in the pulmonary vascular resistance in practically all instances. Although the mechanism by which either drug causes these effects is unknown, we have observed that the prior administration of reserpine abolishes both the transient systemic and the sustained pulmonary arterial hypertension which occurs after the intravenous injection of bretylium (unpublished data). A possible explanation of this difference in action between guanethidine and bretylium may lie in the vascular smooth muscle catecholamine-depleting effect of guanethidine that has been demonstrated by Maxwell and his colleagues[7] and Cass, Kuntzman and Brodie.[8]

Once more it must be explained that these studies, both at rest and during graded levels of exercise, were carried out with the subjects in the supine position. Although this method allowed a study of the hemodynamic effects of the drug uncomplicated by secondary postural changes, one cannot infer from the results the circulatory effects of the drug in subjects in the upright posture, as in ordinary life. Secondly, the drug was administered intravenously and the effects studied within a period of 2 hours. Even though the intravenous route of administration is not the one usually employed therapeutically, the drug is absorbed from the intestines unchanged and the circulatory effects of the oral and intravenously administered drug are likely to be similar except in time-response relationship. The most obvious difference in the circulatory effects of the drug given by these two routes is the frequent and often pronounced bradycardia at rest that follows the oral but not the intravenous route of administration. Again this may be due to the longer action of the drug and the appearance of its reserpine-like features in the former case. However, our studies of the circulatory effects of the orally administered drug have shown no other fundamental differences from those described in the present report. Finally, it must be re-emphasized that the hypertensive patients studied were all without clinical or

laboratory evidence of any cardiovascular disease other than systemic arterial hypertension.

Summary

The effects of the intravenous injection of guanethidine on the systemic and pulmonary circulation have been studied in 4 normal subjects and 12 hypertensive patients at rest and during graded leg exercise in the supine position.

The drug caused a fall in the resting systemic arterial blood pressure and systemic vascular resistance in all subjects; there was a marked quantitative difference in the response of the normal subjects as compared to that of the hypertensive patients, the latter patients exhibiting much greater falls in blood pressure and systemic vascular resistance after a given dose of the drug. Supine leg exercise was not associated with any further fall in systemic blood pressure.

Neither the resting nor the exercising cardiac outputs were affected by the drug in either normal or hypertensive subjects. Although the resting heart rate was unchanged after the drug, there was a relative bradycardia during exercise in both the normal subjects and hypertensive patients after the drug as compared to the control study.

There was a small but definite reduction in the pulmonary vascular resistance without change in the pulmonary wedged pressure in both normal subjects and hypertensive patients. These findings are discussed particularly in comparison with the circulatory effects of bretylium tosylate studied under similar conditions.

REFERENCES

1. Taylor, S. H., and Donald, K. W.: The circulatory effects of bretylium tosylate and guanethidine, Lancet 2:3?, 1960.
2. Fisher, R. A.: Statistical methods for research workers, ed. 10, Edinburgh, 1946, Oliver and Boyd.
3. Page, I. H., and Dustan, H. P.: A new potent antihypertensive drug. Preliminary study of 2-(octahydro-1-azocinyl)-ethyl-guanidine sulfate (guanethidine), J.A.M.A. 170:1265, 1959.
4. Brod, J.: Essential hypertension. Haemodynamic observations with a bearing on its pathogenesis, Lancet 2:773, 1960.
5. Vernikos-Danellis, J., and Zaimis, E.: Some pharmacological actions of bretylium and guanethidine, Lancet 2:787, 1960.
6. Blair, D. A., Glover, W. E., Kidd, B. S. L., and Roddie, I. C.: Peripheral vascular effects of bretylium tosylate in man, Brit. J. Pharmacol. 15:466, 1960.
7. Maxwell, R. A., Plummer, A. J., Schneider, F., Povalski, H., and Daniel, A. I.: Pharmacology of 2-(octahydro-1-azocinyl)-ethyl-guanidine sulfate (SU 5864), J. Pharmacol. 128:22, 1960.
8. Cass, R., Kuntzman, R., and Brodie, B. B.: Norepinephrine depletion as a possible mechanism of action of guanethidine (SU 5864), a new hypotensive agent, Proc. Soc. Exper. Biol. & Med. 103:871, 1960.

Case reports

Tracheoesophageal constriction produced by an unusual combination of anomalies of the great vessels

A case report

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This report is concerned with a description of a patient who presents an unusual combination of congenital anomalies of the great vessels. These anomalies include three of the more commonly recognized vascular rings plus insertion of the ligamentum arteriosum into a coarcted anomalous left subclavian artery. This case illustrates the necessity for considering the existence of multiple congenital anomalies of the great vessels in the same manner as is required in the diagnosis of congenital anomalies of the heart.

Case report

A 7-week-old white male infant was admitted because of rapid respiration and cough which appeared approximately 3 weeks after an uneventful birth by cesarean section. A twin sibling was considered to be normal. One week before hospitalization the patient became cyanotic and apneic after an episode of crying with resultant loss of consciousness for approximately 3 minutes; he recovered spontaneously. Mild cyanosis and dyspnea persisted when he cried. The patient developed a cough shortly thereafter.

The infant weighed 3.76 kilograms. Pulse rate was 140 per minute and regular. Blood pressure was 90 per minute by systolic (flush technique) in both the right arm and left leg. When crying there was a mild generalized cyanosis. The heart was not enlarged grossly but a harsh, Grade 3 long systolic murmur was audible at the lower left sternal border and was transmitted widely over the entire precordium and back. The pulmonic second sound was ill defined. Short paroxysms of a "tight" cough occurred infrequently.

The hemogram showed the following results: hemoglobin, 10.2 Gm. per cent; hematocrit, 23.2 per cent, white blood cell count, 1-,000 per cubic millimeter. Urinalyses was negative for sugar and albumin. The electrocardiogram demonstrated right ventricular hypertrophy. Cardiac catheterization was incomplete because the pulmonary artery could not be entered. However, a large left-to-right shunt at the ventricular level was found, with marked right ventricular hypertension (right ventricular pressure, 90/3 mm. Hg).

Plain x-ray films of the chest showed right ventricular hypertrophy, left atrial enlargement, and pulmonary hypervascularity. These findings were considered to be compatible with ventricular septal defect. X-ray films made with an esophageal barium column (Fig. 1) show an oblique extrinsic pressure defect in the superior mediastinum behind the esophagus, with its lower border on the right and extending superiorly to the left. This pressure defect has the characteristics of an anomalous subclavian artery, but since the direction of the obliquity is opposite to that usually seen in the anomalous right subclavian artery, the coexistence of a right-sided aorta was also suggested. The oblique defect was then attributed to an anomalous left subclavian artery.

Tracheograms show the impression of a right

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Fig. (For legend see opposite column.)

sided aortic arch (Fig. 2 *left*) and narrowing of the trachea shortly below the arch (Fig. 2 *right*).

Serialographic retrograde aortography was performed with the tip of a catheter in the proximal descending aorta. X-ray film made with the ascending aorta opacified (Fig. 3) shows a right-sided aortic arch with a right descending aorta. The details of the vasculature are diagrammed in Fig. 4. The initial vessel which arises from the ascending aorta represents the left common carotid artery arising to the right of the trachea and crossing in front of it. The right common carotid artery is seen next, then the right subclavian artery, and lastly the *left subclavian artery which takes its origin from the* distal arch and is directed behind the esophagus. Fig. 5 shows the ascending aorta emptied of contrast material and again demonstrates the origin of the left subclavian artery from the distal arch and its retroesophageal position. In addition, the anteroposterior x-ray film shows nicely the coarctation of the proximal portion of the left subclavian artery. The artery is markedly dilated proximal to the site of coarctation.

Increasingly more frequent episodes of respiratory distress developed with apnea, cyanosis, and seizures. Paroxysms of coughing usually initiated these episodes, and inspiratory and expiratory wheezes became more noticeable. A thoracotomy through a sternal splitting incision was performed on Oct. 19, 1959, and revealed tracheal compression from an anomalous left common carotid artery anteriorly and the left subclavian artery posteriorly. The ligamentum arteriosum compressed the left lateral aspect of the trachea and the right aortic arch compressed the right lateral portion, thus effecting a constricting ring (Fig. 4). The left subclavian artery and ligamentum arteriosum were ligated and transected.

Postoperatively, there was persistent respiratory distress with inspiratory and expiratory wheezes, and a tracheotomy was performed. Twelve hours later the patient died with primary respiratory arrest.

Autopsy revealed a large ventricular septal defect, right-sided aortic arch, anomalous origin of the left subclavian and carotid arteries as described radiographically, and atelectasis of the lungs.

Comment

The subject of vascular rings has been amply documented in the literature and a complete review of this subject is not indicated here. The reader is referred to the papers of Blumenthal and Ravitch[1] and of Gross[2] for summaries of this subject.

When one considers the frequency of occurrence of the multiplicity of congenital anomalies, it is curious that we do not encounter these complicated situations more frequently. The embryologic basis for the anomalies presented in our patient is diagrammatically represented in Fig. 6.





Fig. 1. Posteroanterior, lateral, and right anterior oblique projections of the chest showing oblique retroesophageal defect indicating the presence of an anomalous left subclavian artery.



Fig 2 Anteroposterior and lateral tracheograms showing the impression of the right side of the aortic arch (*left*) and narrowing of the trachea above the carina (*right*).



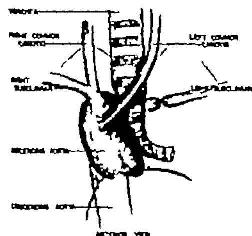
Fig 3 Anteroposterior and lateral aortograms showing right-sided aortic arch and descending aorta retroesophageal anomalous left subclavian artery and anomalous left common carotid artery

The vascular pattern in this patient represents the mirror image of the usual arrangement of right anomalous subclavian artery with additional anomalies of insertion of the ligamentum arteriosum to the site of coarctation of the anomalous subclavian artery The large vessel which gives rise to the left subclavian artery and is proximal to the coarctation probably represents the aortic diverticulum the residuum of the left aortic arch. This anatomic arrangement with anomalous right subclavian arteries has been described previously.[4]

Each of the three vascular rings described in this patient are well recognized entities

1 The anomalous left common carotid artery arises from the aortic arch more to the right than normal and must pass over the anterior surface of the trachea to reach its normal position This usually produces an impression defect on the anterior surface of the trachea.

2 The anomalous subclavian artery arises as the last branch from the aortic arch and passes obliquely across the midline usually behind the esophagus. The position of the defect slightly above the level of the aortic arch and its obliquity usually identifies it. The direction of its obliquity will depend upon its origin from a left or a right aortic arch. Anomalous subclavian arteries are usually incidental



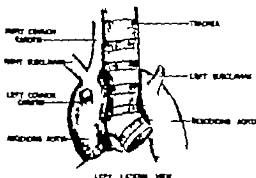


Fig 4 Diagrammatic representation of the vascular anatomy seen in Fig 3.



Fig. 5. Anteroposterior and lateral aortograms showing coarctation of the anomalous left subclavian artery, its retroesophageal position, and its origin from the distal aortic arch.

findings but occasionally produce dysphagia.

3. A right aortic arch with left ligamentum arteriosum or ductus arteriosus may in itself create a ring which encircles the trachea and esophagus. If the ligamentum arteriosum or patent ductus, extends from the pulmonary artery to the left of the trachea and the posterior aspect of the esophagus to join the descending aorta, and is sufficiently taut, compression will result. This was the case in our patient as demonstrated by the findings at operation.

Coarctation of the subclavian artery as well as the insertion of the ductus or ligamentum arteriosum to the site of coarctation are apparently very rare anomalies. The large size of the prestenotic portion of the anomalous subclavian artery probably contributes to the compression of the trachea and esophagus at this level.

Situations of similar complexity will undoubtedly be uncovered with increasing frequency because of our greater concern with surgical correction of these lesions. The embryologic development of the aorta and its branches permits a great variety of possible anomalies. It is suggested that the simultaneous occurrence of several of these anomalies be considered in those cases which do not completely fulfill the criteria for one of the well-recognized varieties.

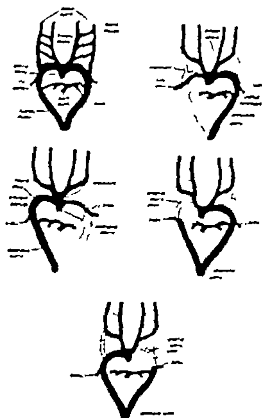


Fig. 6. Embryologic basis for development of anomalies of the aorta and great vessels. *A*, Primitive pattern in which both aortic arches are present with right and left patent ductus arteriosus. *B*, Normal final pattern of aortic system with a *left* aortic arch and left patent ductus arteriosus. *C*, The pattern of right aortic arch and right patent ductus arteriosus. The left fourth and sixth arches have regressed. *D*, The usual pattern of anomalous origin of the right subclavian artery. The right arch is atretic. The right subclavian artery arises as the fourth branch of the aorta. It proceeds upward and to the right behind the trachea to reach its normal position. *E*, The vascular pattern in the patient reported here. This represents a mirror image of the pattern seen in *D* except that it is the opposite right sixth arch (the ductus arteriosus) which remained patent.

Summary

A case which demonstrates an unusual combination of anomalies of the great vessels is described. These include three of the more commonly recognized vascular rings, namely, right aortic arch with left ligamentum arteriosum, anomalous *left* common carotid artery, and anomalous

left subclavian artery An additional anomaly was the insertion of the ligamentum arteriosum to the site of coarctation of the anomalous left subclavian artery and a ventricular septal defect. The importance of considering the simultaneous occurrence of multiple anomalies of the heart and great vessels is emphasized

REFERENCES

1 Blumenthal, S., and Ravitch M M. Seminar on aortic vascular rings and other anomalies of the aortic arch, Pediatrics 20:896, 1957
2. Gross, R. E. Arterial malformations which cause compression of the trachea or esophagus Circulation 11:124 1955
3 Bigo, A., and Dall'Acqua, R. L arteria lusoria Radiol. med. 45:234, 1959

Ventricular aneurysm

Report of a case occurring in a 16-year-old boy with granulomatous myocarditis

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Because the great majority of ventricular aneurysms develop as sequelae of myocardial infarctions, most are found in individuals who are 45 years of age or older. A handful of cases of ventricular aneurysm which occurred in childhood or youth have been reported. The etiology in these cases has been varied and includes congenital defects of the myocardium,[1,2] trauma,[3] rheumatic myocardial necrosis,[4,5] and Chagas' disease.[6] In some cases the etiology of the aneurysm was not apparent.[7] Aneurysms secondary to myocardial infarction have also been described in children. In these cases an anomalous coronary circulation was present.[8] In 102 proved cases of cardiac aneurysm reported by Schlichter and associates[9] the youngest patient was 36 years old, whereas the youngest patient in a series of 26 cases reported by Berman and McGuire[1] was 45 years old. Parkinson's youngest patient in a series of 15 was 30 years of age.[3]

In view of the rarity of ventricular aneurysm in youth, we are reporting the following case.

Case report

R. Y., a 16-year-old school boy, was in good health until August, 1959, when, after an unusually hard day of work pitching hay on a farm, he developed a grand mal seizure. After the convulsion he was admitted to Sacred Heart Hospital, Allentown, Pennsylvania. No abnormal physical or neurological signs were elicited. An electroencephalogram revealed a general dysrhythmia compatible with an idiopathic seizure state. A routine survey chest film was reported as normal, but in a later review of the film a definite bulge was seen on the left lateral wall of the left ventricle. An electrocardiogram was not recorded. He had no more attacks and after a few days of observation he was discharged. He remained in good health for 2 months, at the end of which time he had the first of four episodes of rapid heart action. These attacks lasted about 1 hour and subsided spontaneously. Both the onset and termination of the attacks were abrupt and not accompanied by chest pain. The fourth such episode, which occurred in November, 1959, was accompanied by syncope but no convulsion, and prompted his readmission to the hospital.

Physical examination on admission revealed a well-nourished, pale white boy who was in no distress as long as he remained recumbent. He developed lightheadedness when he sat up. The ventricular rate was 280 per minute. The temperature was 98.6°F., respirations were 24 per minute, and

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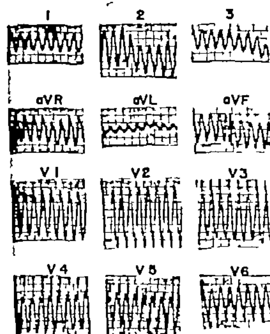


Fig. 1. Electrocardiogram taken Nov. 17, 1959, during an episode of ventricular tachycardia.

blood pressure was 90/60 mm. Hg. No murmurs, rubs, thrills, or gallops were heard. The lungs were clear and there was no peripheral edema. No paradoxical pulsation of the precordium was noted. The remainder of the examination was not remarkable. An electrocardiogram showed ventricular tachycardia (Fig. 1).

One gram of procaine amide was given intramuscularly shortly after he was hospitalized but it failed to convert the ectopic rhythm. Forty-five minutes later he was given 1.6 mg. of lanatoside C intravenously. Fifteen minutes after this injection the mechanism converted to a normal sinus rhythm with very rare ventricular premature contractions. After conversion of rhythm the patient had no complaints except for sticking precordial pains.

The serum glutamic oxalacetic transaminase was 230 units when determined 2 days after he was hospitalized. Two days later it had dropped to 40 units. Chest roentgenography revealed a configuration of the left ventricle which was compatible with a ventricular aneurysm (Fig. 2). Paradoxical pulsation of the bulge on the left ventricular wall was noted on fluoroscopy. The deep Q waves and inverted T waves in Leads I, aVL, V5, and V6 of the postconversion electrocardiograms were also suggestive of a ventricular aneurysm (Fig. 3). He continued to have low-grade fever but the sedimentation rate and C-reactive protein remained within normal limits. Blood sugar, blood count, urinalysis, blood urea nitrogen, and serum cholesterol were all normal.

The patient was transferred to the Jefferson Medical College Hospital on Dec. 2, 1959. Angiocardiograms confirmed the clinical diagnosis of aneurysm of the left ventricle, and he was operated upon on Dec. 17, 1959, by Dr. John Y. Templeton, III.

At the time of operation, the pleural cavities were found to be free of adhesions. Surprisingly there were no intrapericardial adhesions. The aneurysm extended from the anterior descending branch of the left coronary artery laterally and posteriorly about the left ventricular wall and in a transverse direction caudad to the circumflex branch of the left

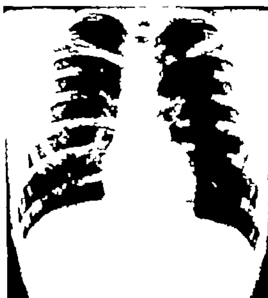




Fig. 2. Posteroanterior (*top*) and right anterior oblique (*bottom*) views of the chest with a barium-filled esophagus, showing the bulge on the anterolateral surface of the left ventricle.

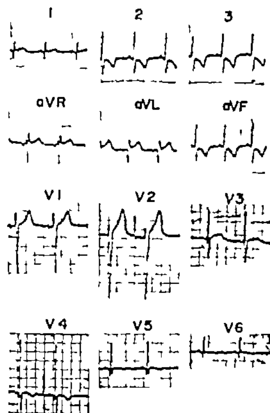


Fig. 3. The mechanism of the postoperation electrocardiogram (taken Nov. 18, 1959) is a normal sinus rhythm with deep Q waves in Lead I and aVL, and smaller but significant Q waves in Leads V_5 and V_6. There is S-T segment elevation in Leads I, aVL and V through V_6. The S-T segment are depressed in Leads II, III and aVF. The T waves are inverted in Leads II, III, aVF and V through V_6. The tracing was interpreted as compatible with a ventricular aneurysm which involved the anterolateral surface of the left ventricle.

coronary artery. The most prominent paradoxical pulsation was in the anterior portion. The wall was grayish white in color composed mostly of thin fibrous tissue but with what appeared to be a few myocardial fibers present. It appeared to be devoid of coronary arteries. Just beneath it lay the great anterior papillary muscle. The lumen of the aneurysm was free of thrombus. The atrial and ventricular septa were intact and there were no anomalous pulmonary veins. The aneurysm was excised with the aid of heart lung bypass with a vertical screen oxygenator.

Microscopic examination of the aneurysmal sac excised at operation revealed moderate diffuse interstitial fibrosis of the myocardium. The myocardial fibers possessed large hyperchromatic nuclei which suggested myocardial hypertrophy. There were a variety of nonspecific degenerative changes, consisting of loss of striations, fragmentation, vacuolization and coagulation of the sarcoplasm without frank necrosis. Focal inflammation of moderate intensity was present in most of the sections. The majority of the inflammatory cells were lymphocytes. In some areas the lymphocytes were seen to be oriented along the margins of degenerated muscle fibers. A few histiocytes and polymorphonuclear leukocytes were also present. Several granulomas were seen appearing as well-delineated foci of histiocytes, epithelioid cells, and young giant cells without necrosis. Some of the cells possessed





Fig. 4. Photomicrograph of the wall of the ventricular aneurysm. *Top* ×200, *Bottom* ×400. There is infiltration with inflammatory cells and granulomas. For full description see text.

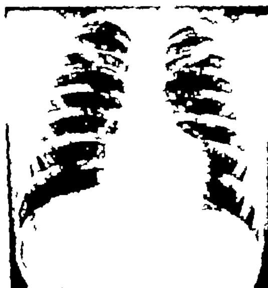


Fig 5 Postoperative chest x-ray film There is a shelving on the left lateral border of the heart at the site of excision of the ventricular aneurysm.

a finely vacuolated cytoplasm which probably contained lipoid material. Acid-fast stains and a Gridley stain for fungi were negative. Careful examination of numerous sections failed to reveal any structures which resembled Toxoplasma or Leishmania. The diagnosis was aneurysm of the left ventricle with chronic focal granulomatous myocarditis of unknown etiology (Fig 4).

Because granulomas were found in the myocardium, skin tests and serologic studies were performed for histoplasmosis, blastomycosis, coccidioidomycosis, and trichinosis. These studies were negative, as was a culture of the myocardial tissue for toxoplasmosis.

The immediate postoperative period was uncomplicated except for development of a pyogenic wound infection, but this responded to drainage and appropriate antibiotics. No later episodes of ventricular tachycardia occurred. The administration of quinidine was continued. When the patient was examined on July 30, 1960, his general condition was good. There was no cough, chest pain, dyspnea, or edema. His activities had been limited up to that date, but a gradual increase in activities was then permitted. In December 1960, he had returned to school and a generally normal existence. A chest x-ray film taken on Dec. 10, 1960, showed that the bulge on the left ventricular wall was no longer present. In its place a small concavity had appeared (Fig 5). The electrocardiogram taken in March, 1960 was quite similar to the tracings taken postoperatively (Fig 6).

Discussion

The diagnosis of ventricular aneurysm in this 16-year-old boy was suspected on the basis of characteristic changes observed in cardiac roentgenograms and electrocardiograms. Cardiac angiography confirmed the diagnosis and the aneurysm was successfully excised with the aid of cardiopulmonary bypass.

The patient had been in apparent good health prior to his convulsion in August 1959. No definite diagnosis was established in regard to the seizure although the electroencephalogram was suggestive of an idiopathic seizure state. The possibility of a ventricular aneurysm had not been considered during his first hospitalization because the abnormal configuration of the photofluorogram was not appreciated. Because of the age of the patient a routine electrocardiogram was not made at that time. Although no more convulsions occurred, it is possible that the seizure resulted from a small cerebral embolus which arose from a clot in the aneurysmal sac. Embolic phenomena of this sort are not uncommon in patients with ventricular aneurysms.[1] In a review of 102 cases of ven

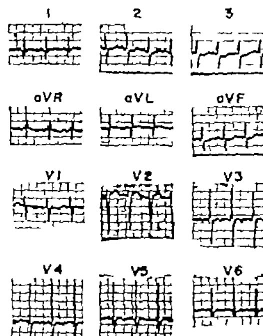


Fig 6 An electrocardiogram taken 3 months postoperatively (March 23, 1960) shows persistent Q waves in Leads I, aVL, V_5, and V_6. The S-T segments are not so much elevated in Leads I and V_6 and are isoelectric in Leads V_1 through V_4. The T waves are now upright in Leads II, III, aVF, and V and are diphasic in Leads V and V_4. The Q-T interval is prolonged, compatible with quinidine effect.

tricular aneurysm after myocardial infarction Schlichter Hellerstein and Katz[9] reported an incidence of thromboembolic phenomena of 51 9 per cent in contrast to an incidence of only 25 6 per cent in patients with myocardial infarction without aneurysm Bertrand and Cooley[11] described a 52-year-old Negro with a ventricular aneurysm who had a similar seizure These authors also considered that a cerebral embolus represented the most likely explanation Berman and McGuire[12] reported on a patient with a ventricular aneurysm who died of emboli to the brain spleen and kidney

Although a grand mal convulsion presumably due to a cerebral embolus, was the initial clinical manifestation of the lesion in this patient it was the paroxysms of ventricular tachycardia that led to his second hospitalization and the correct diagnosis. This type of ectopic rhythm has been associated by others[4,8,13,14] with aneurysm of the ventricle so that when ventricular tachycardia appears in a patient without an obvious cause the possibility of an aneurysm of the ventricle should be considered There has been no recurrence of the ventricular tachycardia in our patient since the aneurysm was removed Couch[14] has also reported a case in which excision of the aneurysm prevented additional attacks of ventricular tachycardia

The cause of the aneurysm in this patient is not clear The patient had no clinical history suggestive of myocardial infarction It is still possible on the other hand that he had a so-called silent infarction from which the aneurysm resulted The microscopic findings of the excised portion of the myocardium are not incompatible with such a series of events, although the fibrosis seen could have resulted from a variety of causes, and it is our opinion that an infarction did not occur The transiently elevated serum glutamic oxalacetic transaminase the low grade fever the episodes of ventricular tachycardia and the presence of inflammatory cells in the histologic sections all suggest activity of the process in the left ventricular wall Although not a common occurrence, myocardial infarction has been reported in infants, children and young adults.[16-19] In some of these cases, congenital anomalies of the coronary circulation existed such as coronary ostial stenosis,[19] anomalous origin of a coronary artery from the pulmonary artery[4] or transposition of the great vessels.[21] Because of limitations imposed by the surgical approach the coronary circulation could not be visualized completely in our patient but it is unlikely that such an anomaly existed The absence of coronary arteries over the aneurysmal sac cannot be considered an anomaly in itself since postinfarctional aneurysms also are usually devoid of arteries Nevertheless, it is quite possible that myocardial ischemia resulted from either premature coronary atherosclerosis or congenital absence of coronary vasculature over the involved portion of the left ventricle leading to fibrosis and aneurysmal development

The finding of granulomas in the myocardium raised the suspicion of an underlying infectious disease Tuberculosis can be excluded in our case because of the negative tuberculin test Sarcoidosis cannot be so easily ruled out despite the absence of other manifestations of the disease Diseases caused by fungi can be largely eliminated because the bacteriologic studies the serologic tests, and the cutaneous reactions for toxoplasmosis, histoplasmosis, blastomycosis, and coccidioidomycosis were all negative

The possibility that the granulomatous foci represented a reaction to the contrast medium used in the angiocardiogram was considered An examination of the slides from three other patients who also underwent angiocardiography prior to the removal of aneurysms of the ventricle failed to disclose any granulomas.

Granulomas without necrosis have been observed in a small number of cases classified variously as isolated myocarditis, Fiedler's myocarditis, or idiopathic myocarditis.[22] In most instances the lesions consist of rather diffuse, nonspecific inflammation with replacement of myocardial fibers, and in those cases with granulomas the term *granulomatous myocarditis* has been used[23] The etiology generally is obscure although an association of granulomatous myocarditis with *thymoma*[24] and penicillin sensitivity[25] has been observed

The question that remains to be answered

in this case is whether the granulomatous myocarditis is the cause or the effect of the ventricular aneurysm It is conceivable that the patient had myocarditis which was severe enough to weaken the ventricular wall but which pursued an entirely subclinical course It is impossible to prove this, and one can take the opposite position equally difficult to prove that the myocarditis followed the formation of the aneurysm representing a response of injured cardiac muscle. Either explanation would be quite unusual

Summary

A report is made of the case of a 16-year-old boy with a ventricular aneurysm complicated by a grand mal seizure and several episodes of paroxysmal ventricular tachycardia. The aneurysm was successfully excised with the aid of cardiopulmonary bypass. A granulomatous myocarditis was found during microscopic examination of the cardiac tissue removed at operation The possible significance of this finding is not clear and we could not determine whether the granulomatous myocarditis was the direct cause of the aneurysm or whether it represented a response to a previous injury to the myocardium

REFERENCES

1 Lovitt, W V J and Lutz, S Jr Embryological aneurysm of the myocardial vessels, A M A. Arch. Path 57:163 1954
2. Grant, R. T An unusual anomaly of the coronary vessels in the malformed heart of a child, Heart 13:273 1926.
3. Hall, D G Cardiac aneurysms, Edinburgh M. J new series 14:322, 1903.
4. Burn, C. G., Hollander A G., and Crawford, J H Rare cardiac aneurysm in a child, Am. Heart J 26:415 1943
5 Parkinson, J., Bedford D E., and Thomson, W A. R Cardiac aneurysms, Quart J Med. 7:455 1938.
6. Mola, B Ventricular aneurysms in chronic myocarditis due to Chagas disease, Rev argent. cardiol. 22 126, 1955
7 Macfie, J W S., and Ingram, A. Three cases of cardiac aneurysm in native boys of the Gold Coast, Ann. Trop. Med. 14 147 1920.
8. Schlichter J., Hellerstein, H. K., and Katz L. N Aneurysm of the heart a correlative study of one hundred and two proven cases Medicine 32:13 1954
9 Walker W J and Richmond G H Posterior ventricular aneurysm in a patient with dextrocardia and situs inversus, Am Heart J 48:275 1954.
10 Berman, B and McGuire, J Cardiac aneurysm, Am. J Med. 8:480, 1950.
11 Bertrand, C A., and Cooley R. N Congenital aneurysm of the left ventricle, Ann. Int. M 43:426, 1955
12 Wasserman, E., and Yules, J Cardiac aneurysm with ventricular tachycardia case report and brief review of the literature, Ann. Int. Med 39:948, 1953.
13 Couch, O A., Jr Cardiac aneurysm with ventricular tachycardia and subsequent excision of aneurysm case report, Circulation 20:251 1959
14 Dick, M. M. Aneurysms of the posterior ventricular wall, South M J 48:465 1955.
15 Hunter A. L., and Insall, J N Myocardial infarction in a young adult, Brit M J 1 1282, 1959
16. Pomerantz, H Z., and Scheiner N Myocardial infarction associated with hypercholesterolemia in a young eunuch, Canad. M.A J 80:362 1959
17 McVay L V J Myocardial infarction in young men, Postgrad Med. 20:506, 1956.
18. Ravich R. M and Rosenblatt, P Myocardial infarction in the newborn infant, J Pediat 31:266, 1957
19 Roth O and Pepe, A. V Myocardial infarction in young males, Connecticut M J 21 12, 1957
20. Goormaghtigh, N DeVos, L., and Blancquaert, A Ostial stenosis of coronary arteries in a nine-year-old girl, A M A Arch Int Med. 95:341 1955
21 Berureiter M Myocardial infarction in an infant with transposition of the great vessels J.A.M.A. 167:459 1958
22. Tesluk, H Giant cell versus granulomatous myocarditis, Am. J Clin. Path 26 1326, 1956
23 Saphir O Myocarditis a general review with an analysis of 240 cases, A.M A. Arch. Path. 32 1000 1941
24. Langston J D Wagman, G E and Dickenman, R. C. Granulomatous myocarditis and myositis associated with thymoma, A M A. Arch. Path. 68:367 1959
25 Waugh, D Myocarditis, arteritis, and focal hepatic splenic, and renal granuloma apparently due to penicillin sensitivity Am. J Path. 28:437 1952.

Clinical pathologic conference

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Clinical abstract

History. A 4-year-old white girl who had previously been quite healthy developed a swelling of the left side of the face and slight fever which was considered to be mumps. Five days after the onset of the facial swelling, she developed generalized edema which progressed until 5 days later when she was admitted to a local hospital. Here she was considered to have congestive heart failure, and was digitalized and given oxygen. She was discharged 10 days later. Five days after discharge she was readmitted with supposed rubeola and a return of all symptoms. She improved on 0.15 mg. of digoxin daily and was transferred to the Research and Educational Hospitals for additional study.

Her past history was not contributory. She had developed well, had never had any heart murmurs, cyanosis, or clubbing, and had always been active. A sibling had died from cardiac arrest during repair of an umbilical hernia, and a paternal grandparent had a coronary occlusion when he was 50 years old.

Physical examination. On examination she was found to weigh 34 pounds; she had no complaints and was in no apparent distress. Her pulse was 140 per minute, respirations were 35, and blood pressure was 90/70 mm. Hg. Abnormal findings were limited to the cardiovascular system. There was a slight precordial bulge with enlargement of the heart. The point of maximal impulse was near the anterior axillary line at the level of the fifth left intercostal space and was heaving in character. S_1 was not muffled but of normal intensity and maximal at the apex. S_2 was of normal intensity, normally split, and maximal at the upper sternal border. *A gallop rhythm was heard over the entire* precordium, maximal at the apex and left sternal border. The edge of the liver was 2 cm. below the right costal margin. There was no venous engorgement and no arterial pulsation.

Laboratory data. The electrocardiogram showed *low T waves in Leads I, aV_L, and V_6, and inverted* T waves in Leads II, III, aV_F, and V_6. The S-T segment was depressed in Leads II, III, and aV_F. The amplitude of the S wave in Lead V_1 was border-line normal (Fig. 1). Roentgenograms of the chest revealed an absence of abnormal vascular pattern, infiltrates, or effusions, but a generalized globular cardiomegaly. The cardiophrenic angles were sharp. The blood showed hemoglobin of 9.2, hematocrit of 37, and white blood cell count of 10,500. The urine was normal, as were the serum Na, K, cholesterol, total protein, A/G ratio, bilirubin, blood urea nitrogen, Bromsulphalein retention, serum glutamic oxalacetic transaminase, prothrombin time, Cl, CO_2, serology, blood cultures, electrophoretic patterns, and lupus erythematosus preparations. The thymol turbidity was 7.2 units, and the cephalin flocculation was 3+ on the day of admission but negative later. The alkaline phosphatase was 2.6, and the antistreptolysin-O titer was 12 units.

Hospital course. Digitalization and bed rest were continued. Pericardiocentesis was performed but no fluid was obtained. She had a fever which reached 104° F. for several days. It responded to Chloromycetin, 175 mg. intramuscularly every 6 hours. She was given a diet which was low in sodium, and injection of Mercuhydrin, 0.25 c.c. intramuscularly, was started. However, her condition continued to deteriorate slowly. She would have episodes of tachypnea and orthopnea, with no evidence of cardiac failure except for an increase in gallop rhythm. Prednisone, 5 mg. twice a day, was also begun 3 weeks after she was hospitalized. During her final week of life she complained of abdominal pain and nausea. There were periods of apnea. She died 1 month after admission.

Discussion

DR. ROBERG. This child was ill for only 2 months. During the first month she became edematous on two occasions. Each time the edema followed an acute infection, first mumps and then measles. Both episodes of edema cleared rapidly when she was treated with bed rest and digitalis. After recovering from the second episode of congestive failure, she was transferred to this hospital for study.

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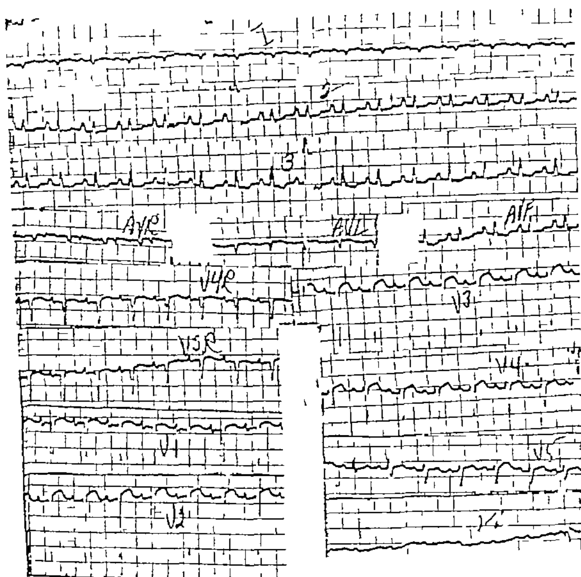


Fig. 1. Normal sinus rhythm electrically vertical heart. Atrial and ventricular rates of 145 per minute. Minimal R waves without progression and upright T waves from Lead V$_{4R}$ through Lead V$_4$. Abnormally small amplitude of QRS complexes in the limb leads, unipolar extremity leads, and Leads V and V$_6$, with flat or diphasic T waves.

While she was under constant bed rest and treatment, her condition steadily worsened and with episodes of tachypnea and dyspnea associated with a gallop rhythm she died at the end of the second month. Her physical and laboratory examinations gave normal findings, except for a slight precordial bulge, marked globular cardiomegaly, tachycardia, a heaving precordial impulse, triple rhythm and a pulse pressure of 20 mm. of mercury. There were no murmurs, the pulmonic second sound was normally split and of normal intensity, the pulmonary vasculature was normal radiologically, and the electrocardiogram showed no evidence of preponderant ventricular hypertrophy or left ventricular ischemia.

We are faced with the problem of heart failure which was in the first month not severe, alarming, or refractory to treatment. Originally, the child was not hospitalized until she had been edematous for 5 days, which implies that she was not

dyspneic. And after her rapid improvement within 10 days, she was sent home without continued digitalization. Our first thought, of course, is that of an acute viral myocarditis associated with mumps. If this were an acute viral myocarditis developing in a heart which was normal until then, the myocarditis would need to be very severe in order to cause prompt congestive heart failure and edema. Such severe viral myocarditis, analogous to severe rheumatic and diphtheritic myocarditis, is usually associated with alarming illness and dyspnea, and is refractory to treatment. In chronic heart disease, on the other hand, a mild or transient insult to the myocardium or a burden upon the circulation can precipitate mild congestive heart failure which responds quickly to routine therapy. These considerations lead me to believe that this child's illness did not represent uncomplicated viral inflammation of a previously normal heart.

There is no evidence either of valvular disease or of congenital septal or vascular abnormalities. Her age and the lack of stigmata of ischemia in the electrocardiogram militate against an anomalous origin or calcific occlusion of the left coronary artery. There is no evidence of diffuse vascular disease, and thus no reason to consider such conditions as hypersensitivity angiitis, systemic lupus erythematosus, or periarteritis nodosa. Nor is there disease of other systems which might suggest glycogen storage disease or muscular dystrophy.

We need consider seriously only primary diseases of the pericardium, myocardium, or endocardium. Such diseases are associated with abnormal ventricular filling and consequently a prominent gallop rhythm. The tachycardia, low pulse pressure, and paroxysmal dyspnea would be consistent with failure of the left ventricle either to fill or to empty properly.

Although the heaving cardiac impulse, the sharp and acute cardiophrenic angles, and the dry tap of the pericardium do not exclude pericardial effusion, they render effusion improbable. There were no stigmata of cardiac tamponade. Primary tumors of the pericardium and of the myocardium are rare at this age, as are intra-atrial myxomata. I will not discuss them except to note that tumors can cause the gradual onset of heart failure which rapidly becomes relentless.

There are only two conditions upon which I would like to speculate— endocardial fibroelastosis and chronic granulomatous myocarditis. With respect to myocarditis, one might postulate that there was indeed a mild viral myocarditis antedating the onset of the edema, that antibodies developed against myocardial antigen, and that a progressive "autoimmune" granulomatous myocarditis led to her death. "Autoimmune disease," not without reason, is in vogue, with interesting but inconclusive observations on antibodies to myocardium. The reopening of the question of the myocardial origin of the Aschoff body and the immunologic studies of thyroiditis, glomerulonephritis, and systemic lupus erythematosus lead one to wonder whether such a mechanism may not in the future explain some of the unclassified types of "degenerative" or metabolic myocardial failure.

Despite the attractiveness of the diagnosis of acute myocarditis, the mild and gradual onset of her illness speaks strongly against that diagnosis. The most common disease which affects the myocardium or endocardium at this age, excluding rheumatic fever, is endocardial fibroelastosis. With the onset of heart failure the course often is rapid and refractory to treatment. In keeping with the suggestive evidence that this child had pre-existing disease, I believe it is most likely that she suffered from endocardial fibroelastosis. The two infections at the onset of her illness may have been coincidental and irrelevant. On the other hand, the infections may have precipitated failure, as can any infection, or there may have been a mild viral myocarditis superimposed upon the underlying heart disease.

DR. LEARY: We have only the chest films taken in this hospital, not that from the local hospital.

From the time of the first examination until the final examination the x-ray films showed very few, if any, changes. In one of the initial films, an upright chest film, there was a so-called globular heart (Fig. 2). There was obvious enlargement of the heart, but no specific chamber could be



Fig. 2. X-ray view of chest, upright position, showing an enlarged heart which is globular in shape.

outlined. In the lateral film there was the same marked cardiac enlargement and no specific chamber that could be detected. The posterior cardiophrenic angle in the lateral film was still quite sharply defined and acute. In the anteroposterior film there were good cardiophrenic angles which served as guides in the evaluation of whether this was an enlargement due to an effusion.

The radiologic differentiation between cardiac enlargement and pericardial effusion is a very uncertain one. One method has been described recently. Because of the fact that usually in pericarditis there is loculation of fluid and displacement of the heart backward, lateral kymographs will show some damping of the anterior pulsations with good filling of the esophagus if a barium swallow is given at the same time. In this case we tried another method which we believed might be less trying to the patient and that was the introduction of air into the pericardium.

DR. ROBERG. Unless you are sure you are in the pericardial sac you don't know where you are putting it. How do you feel about inserting a catheter into the right atrium to determine whether there is an effusion?

DR. LEARY. That would certainly settle it very quickly. Some people also have suggested the introduction of carbon dioxide intravenously, the same effect is produced and then the distance between the negative and the filled layers or areas can be outlined.

DR. ROBERG. You don't think that this is dangerous?

DR. LEARY. No.

DR. ROBERG. How much carbon dioxide do you inject?

DR. LEARY. I don't remember the exact amount, but it is about 100 c.c.

Another method of radiologic differentiation is to contrast the film made when the patient is in the recumbent position with that made when the patient is in the upright position, to see whether there is any change in the size of the heart, on the theory that if fluid is present in the upright position it will settle toward the base of the heart in the recumbent position. In the two films taken with the patient in those positions I do not believe that there was any change in the cardiac contour.

DR. KRAKOWER. This child at the time of autopsy was of relatively normal length (103 cm.) and weight (35 pounds) for a child of her age. There was no peripheral edema. However, the peritoneal cavity contained 250 c.c. of clear, straw-colored fluid. The pleural cavities each contained 20 c.c. of a similar fluid. The thymus was a little reduced in size.

The pericardial sac contained 40 c.c. of bloody fluid. Intracardiac adrenaline had been administered a day before death. Therefore it is uncertain how much fluid had been in the pericardial sac prior to the injection.

The heart was considerably enlarged. It weighed 180 grams, as compared with 73 grams for a normal child of 4 years of age. It was globular in shape, the apex was formed by the left ventricle. There were faint grayish patches over the epicardium with multiple hemorrhages, including one at the site of puncture of the left ventricle. The enlargement of the heart was at the expense of both ventricles. The atria were not enlarged, although there was some thickening of their walls, particularly of the left atrium, which measured 0.15 cm. in thickness. Their endocardial surfaces were normal. The right ventricle was markedly enlarged. In the fixed state the inflow tract measured 5.0 cm. in length and the outflow, 6.5 cm. The maximum

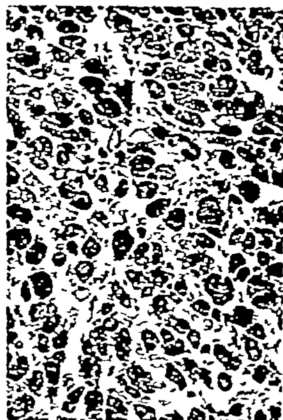


Fig. 3. Microscopic view of the myocardium of the left ventricle, revealing hypertrophied muscle fibers with fine diffuse interstitial fibrosis. Note the displacement of the capillaries away from the muscle fibers with apparent thickening of their walls. Hematoxylin-eosin; magnification, ×250.

transverse diameter at the base of the ventricle on its septal aspect was 5.5 cm. There was some thickening of the trabeculae carneae but the endocardium was normal. The thickness of the wall of the right ventricle at its base in the inflow tract was 0.3 cm., and in the outflow tract, 0.4 cm., whereas at the apex the thickness was reduced to 0.2 cm. The enlarged left ventricle presented thick papillary muscles, with, at best, slight endocardial thickening over these muscles and elsewhere—certainly not in keeping with endocardial fibroelastosis. There were multiple mural thrombi particularly between the trabeculae carneae anterolaterally. Inflow and outflow tracts of the left ventricle measured 6.0 cm. from base to apex, with a transverse septal diameter of 5.5 cm., similar to that of the right. The thickness of the myocardium was 0.8 cm. at the base, both of the inflow and outflow tracts, and from 0.2 to 0.4 cm. close to the apex of the ventricle.

All valves showed moderate thickening of the cusps, the result of hemodynamic changes. However, they all presented smooth endocardial surfaces with no vegetations, adhesions, or defects. There was circumferential widening of the tricuspid and pulmonic valves particularly, which measured 8.5 and 6.0 cm., respectively. The mitral and aortic valves measured 7.5 and 4.5 cm., respectively.

The myocardium of the left ventricle was firm and red, with diffuse fine whitish streaking. The coronary arteries were larger than expected for a normal heart at this age. There were neither valvular nor intimal coronary atheromatous lesions. The ascending arch of the aorta measured 3.5 cm. in circumference, the thoracic aorta 2.6 cm., and the abdominal aorta at the level of the renal arteries 1.8 cm. There were no atheromatous lesions.

As for the other organs, the lungs were heavier than normal. The right lung weighed 160 grams, as compared with a normal weight of 90 grams. The left lung weighed 120 grams, as compared with a normal weight of 83 grams. There was a fair amount of atelectasis. The lungs were congested, and there was a modest amount of edema.

The spleen weighed 50 grams (normal 38 grams). The pulp was dark red. Follicles were preserved.

The liver weighed 550 grams (normal 516 grams). It was light reddish-brown externally, and, on section, was congested with a yellowish tinge.

The kidneys weighed 59 grams each; they were within the normal range of weight and showed some cortical congestion.

The other organs were not remarkable. The brain was not examined.

Microscopically, the myocardium of the left ventricle showed hypertrophy of muscle fibers with a fine to coarse pencilled interstitial fibrosis of varying degree throughout (Fig. 3). Associated with the fibrosis, there was displacement of the capillaries from their normal close proximity to the muscle fibers. These vessels appeared to be thickened. There was little fibrosis in the auricular or right ventricular myocardium except for one focus of mononuclear-lymphocytic infiltration about a

necrotic muscle fiber. The few myocardial cellular infiltrates seen elsewhere were closely related to either the light cellular reaction in the epicardium or the reactive changes associated with the mural endocardial thrombi. In nonthrombotic areas there was, at best, mild fibroelastic endocardial thickening. In areas with mural thrombi there was monocytic-lymphocytic and eosinophilic infiltration of the adjacent endocardium and myocardium. There was variable organization of the thrombi associated in places, with heavy polymorphonuclear infiltration. No bacteria were recognizable in these latter areas.

There was no demonstrable lipid in the muscle fibers. There were, however, abundant fat-laden histiocytes at the base of the mural thrombi.

In the lungs there was bronchiolectasis, with some centrolobular emphysema. Some of the smaller bronchi were dilated and filled with mucus and/or macrophages. There was alveolar septal vascular congestion with, in some areas, abundant alveolar phagocytes, and in other areas, edema or red blood cell extravasation. The lymphatics were wide in all sections of lung that were examined.

The liver showed more acute congestive changes, with atrophy of the centrolobular cords of cells and widened sinusoids. This was variable, however, and in places there was mild fatty metamorphosis which progressed to necrosis of the liver cells with only mild sinusoidal widening. In other areas the liver cells had disappeared and the expanded sinusoids occupied the space vacated by them. There were periodic-acid Schiff-positive granules in the periportal liver cells. These stained faintly for glycogen with Best's stain.

In the kidney there was appreciable congestion and enlargement of the glomeruli as well as congestion of the vessels in the outer portion of the medulla.

There were so-called toxic changes in the follicles of the spleen and lymphoid tissues generally, and in the former organ there was sinusoidal congestion with early fibrous thickening of the perisinusoidal walls.

The other organs were not remarkable microscopically, except for edema of the adventitia of the gall bladder, a cellular bone marrow—predominantly granulocytopoietic—and evidence of lines of arrest of growth, but, at the time of death, renewed fairly active endochondral ossification at the epiphyseal plates.

In summary, there was marked cardiac ventricular dilatation with quite marked hypertrophy, particularly of the left side, associated with mural thromboses. There was diffuse fibrosis throughout the left ventricular myocardium, with little active cellular infiltration. That which was present, except in one instance, could be related to reactive changes in epicardium and in the endocardium, the seat of thrombosis. There were acute to chronic congestive changes in lung, liver, spleen, and kidneys, associated with a moderate amount of ascites.

The interest of this case lies in the lesson to be learned in the taking and accepting of a clinical history. This child was supposedly well until she developed a fever with swelling of the face. Mumps was prevalent in the community at the time, and it was natural for the family to assume that this too was mumps. Five days after the onset of this illness, when the child was admitted to another hospital in cardiac failure, there was doubt in the mind of the physician that the child had mumps, even though it would have been easy to have accepted this as a rare case of mumps myocarditis with cardiac failure. Accordingly, he submitted blood and stool for viral studies to the Illinois State Virus Laboratories. The stool was cultured with monkey kidney cells but there was no evidence of cytopathogenicity. With the serum, complement fixation tests were performed with poliomyelitis viruses II and III, which yielded titers of <8 in all cases. It was also tested against Coxsackie viruses E9, B3, B4, and B5, which yielded titers of <8 in all cases, with Herpes virus <32, and with mumps (soluble) <16. At the time of the second hospitalization, there was no evidence of a rubeolar rash, and the physician again doubted the association of recurrence of cardiac failure with the history of measles as given by the family.

The doubt whether mumps was a causative factor in this child's cardiac disease continued to plague the physician

here and at the time of death there was enough uncertainty about this that pericardial fluid and a sample of myocardium were submitted to the Illinois State Virus Laboratories for additional viral studies. These were cultured with monkey kidney cells on chick embryo and were injected into baby mice the results in all instances were negative.

It seems unlikely in retrospect and in view of Doctor Roberg's critical clinical analysis that this child had a mumps myocarditis which after a lapse of 4 months presented itself as an enlarged hypertrophied heart with diffuse myocardial fibrosis.

It seems to be more appropriate to accept the view that this child had an idiopathic cardiac hypertrophy in which cardiac failure was precipitated by two successive febrile illnesses of uncertain type. The myocardial fibrosis too by its distribution and nature can be more readily explained on the basis of relative coronary insufficiency in view of the hypertrophy rather than on the basis of scars which were the result of inflammatory infiltrates.

Diagnosis Cardiac hypertrophy presumably idiopathic with cardiac failure precipitated by febrile illnesses of uncertain nature

Annotations

Should the patient with mild hypertension be treated?

Should the asymptomatic patient with mild or moderate essential hypertension be treated for his disease? It has often been stated that these patients need not receive treatment if they fail to show progressive hypertensive cardiovascular disease. "Treat the patient, not the blood pressure!" we have been admonished.

The danger of elevated blood pressure can be determined only by an objective statistical analysis of the fate of large numbers of hypertensive patients. New data on the relation of systolic and diastolic pressures to mortality are available from the Society of Actuaries Build and Blood Pressure Study 1959.* This extensive study, based on several million people insured by 26 large life insurance companies, demonstrates that in all age groups the mortality ratios show a pronounced upward trend with even minimal increase in *either* the systolic or diastolic blood pressure, and a more rapid rise with elevations of both. For example, individuals insured at ages 40 to 49 with systolic pressures of 148 to 157 mm. Hg and diastolic pressures of 93 to 97 mm. Hg had three times the mortality rate of standard risks. Furthermore, the study gives clear evidence that blood pressures below average are associated with the lowest mortality. Men with systolic blood pressures of 98 to 127 mm. Hg and diastolic pressures of 48 to 67 mm. Hg had only 75 per cent of standard mortality." Some have argued that the blood pressure recorded in the physician's office does not represent the patient's true value. However, it was precisely such determinations of blood pressure that correlated so closely with future mortality.

Figures are not yet available to demonstrate that a lowering of the blood pressure of patients with moderate hypertension lengthens life. Statistics do indicate that a lowering of the blood pressure of patients with malignant hypertension prolongs survival. It seems reasonable that therapy instituted early in the course of hypertension, before damage to vital organs has occurred, might be even more effective.

In view of the marked increase in mortality associated with moderate elevation of systolic or diastolic blood pressure, it is suggested that all patients with primary hypertension should not only receive treatment but should be followed up to insure that their blood pressure remains within a normal range.

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Touring and electrocardiograms

Most of the people over the age of 50 or 60 who, while undertaking rather long trips, have the misfortune to need the help of a heart specialist during the course of their travel have had in their past one medical check up with an electrocardiogram. In fact, a fair number of these people had a routine examination just before they started their trip.

They seldom carry an electrocardiogram with them; they sometimes exhibit a medical report, but most often they have no such records at all with them. If any heart inconvenience happens to occur on their way, a comparison of the present findings with a previous report and electrocardiogram could be quite valuable. Therefore, we would recommend that any person older than, let us say, 50, and anyone who has suffered from heart disease, be advised to carry on his trip abroad a copy of the last electrocardiogram that was recorded. That such a precaution should be disregarded for psychological reasons should be fairly uncommon. There is certainly small likelihood that coronary heart disease will develop during a trip of a few weeks, but, in our opinion, it does occur often enough with regard to the thousands of people traveling nowadays to

warrant such an advice. In most cases there is great difficulty in obtaining a previous electrocardiographic tracing within a few days, either from the patient's physician or from the hospital where it was recorded.

After writing these lines, we were advised of L. E. Lamb's article (*Aerospace Medicine* 31:856, 1960) which expresses the same opinion as ours. Lamb's presentation of his pocket electrocardiogram appears to be a very complete and practical solution.

We also would greatly appreciate knowing what other physicians think in this respect, their objections as well as their suggestions, in order to clarify this problem.

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The WPW syndrome

The electrocardiographic pattern of anomalous atrioventricular excitation continues to elude diagnosis in a surprisingly large number of cases. Although there are many clues that suggest the syndrome, correct interpretation of the electrocardiogram remains the only way of making the diagnosis, for the Wolff-Parkinson-White syndrome is unique in that its diagnosis depends entirely on the electrocardiogram. If a few simple facts are remembered, the diagnosis can be made easily in all save an occasional case which requires special study. The syndrome should receive serious consideration whenever the following clues are noted: (1) P-R interval of 0.12 second or less and an abnormal QRS complex; (2) runs of abnormal ventricular complexes at extremely fast rates during paroxysms of atrial fibrillation; (3) ventricular pattern which suggests bundle branch block; (4) a change in the features of the tracing either spontaneously or in response to certain procedures, especially if the duration of the P-R and QRS intervals change in opposite direction; (5) heavily slurred initial component of the QRS group of deflections; (6) occurrence or history of paroxysmal tachycardia.

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CEPTS. By Andres Goth, M D., Professor of Pharmacology and Chairman of the Department, University of Texas Southwestern Medical School, Dallas, Tex. St. Louis, 1961 The C. V Mosby Company 551 pages. Price $11

As the author points out in the preface of this book, the knowledge concerning drugs and their actions increases daily because of the rapid growth of research in medicine. However the fundamental precepts of the mode of action of drugs do not increase so rapidly Advances in knowledge of the mode of action of drugs depend upon advances in biochemistry and physiology and then upon application of this knowledge to the field of pharmacology The author states that it is his intent in writing this book to teach the principles and concepts of pharmacology rather than the factual information about the actions of drugs. It would seem to this reviewer that even though the author has made considerable advances in this direction over currently available texts on pharmacology there are areas which could be improved.

The content of the book follows that used by most medical schools in an introductory course to pharmacology The factual material is good in most areas, but there is very little connection made for the student between pharmacologic action and therapeutics. Most likely this was intended by the author since the aim is to teach the fundamentals of pharmacology but this limits the usefulness of the book as a reference work for the physician.

In the opinion of the reviewer this book is currently the best attempt at presenting the precepts of pharmacology with some fundamental knowledge about the actions of classes of drugs. However the teacher is still left with the problem of whether to teach a medical class the fundamentals of pharmacology or the fundamental pharmacologic basis for therapeutics.

CARDIOPERICARDIOMYOPEXY A NEW SURGICAL TREATMENT FOR HEART DISEASES. By Dr Aaron N Gorelik, New York, in collaboration with Prof Camille Lian, Paris, Prof. Louis Thiebiot, Clermont Farrand, Dr Mendel Jacobi, New York, Dr Ralph Ricciardi, New York, and Dr Madeleine Hascher Paris. Revised English edition of *La Cardiopericardiomyopexie*, Paris, 1956, Expansion Scientifique Française. New York, 1960 The Myopexy Association of the State of New York, 176 pages, 30 illustrations.

This book is a revised English edition of a treatise which was originally published in 1956. Three of the six collaborating authors are Frenchmen, and the other three are New Yorkers. The specific purpose of the book is to ballyhoo the operation of cardiopericardiomyopexy as done by the late Dr Aaron N Gorelik, as a "new treatment for heart diseases." This surgical procedure is to be differentiated from cardiomyopexy as first performed on human beings by Dr Claude Beck done by Dr S. A. Thompson (1935). Dr Gorelik is reported to be the first to combine these operations. However since this was done in 1949 it can hardly be accepted as a "new" form of treatment at a time when one expects to see the description of an original heart operation in each new issue of the surgical journals. Whether or not cardiopericardiomyopexy is a good operation is not within the province of this reviewer to discuss. The authors give considerable experimental histologic, and clinical evidence to support their claim, but there are no comparisons with other procedures advocated for myocardial revascularization. The operation is reported to have been helpful in the treatment of valvular disease, septal defects, and heart block, in addition to angina pectoris. This panacean effect seems almost too good to be true. Even Dr Gorelik himself is stated to have been rehabilitated by it.

One third of the book deals with surgical technique and evaluation of the results, and the rest of the book deals with the diagnosis of disease for which the operation is proposed and various aspects of the coronary circulation. The reviewer thought that the chapter on the pathology of coronary and rheumatic heart disease is the most interesting one.

This book will be of some interest to cardiologists and cardiac surgeons, but the reviewer believes that its greatest value is as a memorial to Dr Aaron N Gorelik, since it was published by his very grateful patients who formed a group known as the Myopexy Association of New York.

HYPERTENSION VOLUME IX CHEMICAL AND HORMONAL FACTORS (Proceedings of the Council for High Blood Pressure Research, American Heart Association). Edited by Floyd R. Skelton, M D Ph.D Research Director The Urban Maes Research Foundation, and Associate Professor of Pathology Louisiana State University School of Medicine, New Orleans, La. New York, 1961 American Heart Association, Inc Price $2.50.

The papers which comprise this volume fall into three groups. The first is concerned with catecholamine metabolism, in which the importance of metabolic inactivation of epinephrine and norepinephrine by means of O-methylation is stressed. A second group of papers centers around problems of vascular reactivity and the pressor activity of angiotensin and some of its analogues. A difference in the reactivity of veins to angiotensin in normotensive and hypertensive populations is shown. The final group of papers deals with an apparent interrelationship between the production of renin and the excretion of aldosterone. Infusions of angiotensin stimulate the secretion of aldosterone. It is suggested that the elevated secretion of aldosterone seen in severe and malignant hypertension may be explained on this basis. In general, the papers are written succinctly and with clarity. The subject matter should be of interest to a wide readership.

Announcements

THE NINTH CONGRESS OF THE PAN PACIFIC SURGICAL ASSOCIATION will be held November 5 through 13 1963 in Honolulu, Hawaii

For further information, write to Dr F J Pinkerton, Director General, Pan-Pacific Surgical Association, Suite 570 Alexander Young Bldg Honolulu 13 Hawaii

THE HEART ASSOCIATION OF SOUTHEASTERN PENNSYLVANIA announces a two-day Scientific Session on "The Application of Computers in Cardiovascular Disease" to be held at the Sheraton Hotel, Philadelphia, Pa Feb 27 and 28, 1962.

The sessions include Introduction to Computer Analysis Application of Computers in Biomedical Science Application of Computers in Cardiovascular Research Application of Computer in Cardiovascular Diagnosis Use of Computers in Hospital Administration and Use of Computers in Psychiatry (The latter session is tentative.)

The chairman will be John H Moyer M D Professor and Chairman Department of Medicine Hahnemann Medical College and Hospital, Philadelphia, Pa

For programs and reservations contact H. Donald Burr Program Director Heart Association of Southeastern Pennsylvania 318 South 19th St Philadelphia 3 Pa Phone PEnnypacker 5-3865.

American Heart Journal

March 1962 Volume 63 Number 3

Editorial

Peripheral circulation in cold climates

Jacques LeBlanc Ph D
Quebec Canada

The primary factors which control blood flow in the extremities are blood pressure and resistance These in turn are affected by many internal and external factors. The decreased blood flow observed in a cold environment is caused mainly by an increased peripheral resistance However repeated exposures of the extremities to low temperatures gradually minimize the response so that after a while the skin does not cool so much This adaptation was observed in Eskimos[1] as well as in white people as we have shown recently Before discussing this adaptation let us consider what happens in the extremities when they are cooled. First there is a direct effect which persists even in sympathectomized hands. This effect which consists of a vasoconstriction of the arterioles induces a decrease in blood flow Similarly the increased viscosity of blood caused by low temperatures diminishes directly the flow in the extremities. There are also nervous control mechanisms which accentuate this change in blood flow Indeed the cutaneous neuroreceptors send afferent impulses to the central nervous system and the efferent impulses which originate from the hypothalamus are transmitted through the sympathetic neural system to influence the vascular tone Furthermore if the surface of the skin which is cooled is sufficiently large to induce even minor changes in the temperature of the blood which reaches the highly vascularized centers of the hypothalamus a decreased peripheral blood flow may result. All these factors which diminish blood flow induce a negative heat balance in the extremities which explains the lowering of the temperature of the tissues. It seems that when the extremities are cooled the first impulse so to speak, of the organism is to protect the core i.e the vital organs. However after a few minutes if the body remains in a neutral thermal state the cooled extremities are allowed to rewarm through a cold induced vasodilation which is due to an increased flow through the arteriovenous anastomoses. In the case of the hand immersed in ice-cold water the temperature of the skin may be as low as that of the water but this cold dilatation is often sufficient to increase it by 3 or 4 degrees Fahrenheit. With this slight elevation in the temperature of the skin this extremely painful stimulus may become a sensation to which the individual is completely indifferent even when the hand is maintained in ice water The adrenergic response which results from this stimulus is the basis of the cold pressor test described by Hines[2] for depicting exaggerated adrenergic response Consequently

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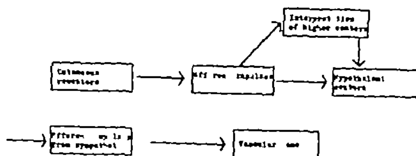


Fig. 1. Possible mechanisms of adaptation in the vascular response to repeated stimulation of the cold neuroreceptors.

as was stated by Grant and associates[4] 30 years ago, the cardiovascular response to this painful local stimulus is characterized by a marked local decrease in blood flow as well as a general peripheral vasoconstriction initiated by sympathetic stimulation.

Let us now consider the phenomenon of adaptation which has been observed after many exposures of the extremities to a cold environment. We know that Eskimos have a better blood flow than have white people, maintain a good manual dexterity in cold weather, and are less sensitive to frost bite.[1-3] Recently, we have shown that adaptative changes also develop in white people. Fishermen from Gaspé in Quebec repeatedly immerse their hands in water at about 30 degrees Fahrenheit during the fishing season, which lasts from April to December. When these fishermen were compared to a group of control subjects, they responded quite differently to a cold water test. They were shown to maintain a higher skin temperature and blood flow, to experience a much lower pain sensation, and to have a smaller increase in blood pressure than did the control subjects.[6]

This study shows that repeated stimulations of the cold neuroreceptors cause an adaptation in the vascular response. Since the mechanism of this adaptation is still unknown, the many possibilities illustrated in Fig. 1 are suggested.

As we see, it is possible that the cutaneous impulses in these adapted people are weaker or that the efferent impulses are not so strong because of some changes in the hypothalamus or a different interpretation from the higher centers. This last possibility is suggested by the mental attitude of these fishermen toward the stress to which they were exposed. Indeed, they already knew in their minds the measures and intensity of this stress, and they were sure that no harm would result from it.

When a cold pressor test is carried out on a group of people who are not adapted to this stimulation, a wide variety of responses is obtained. Some individuals will show maximum cardiovascular reactions, whereas others will react very mildly. Studies have shown that the high-responsive individuals as a group are sympathicotonic, whereas the low-responsive individuals are vagotonic. The criterion used to classify individuals into these two groups was the response to injected adrenaline.[7] It would be interesting to find out whether people who are adapted to this cold pressor test, and who have become low-responsive individuals, like the fishermen of Gaspé, would at the same time become less responsive to adrenaline. In other words, would adaptation to this stress confer to individuals a general vagotonic predominance? If this phenomenon should fail to occur, then the conclusion would be that adaptation induces a decreased cardiovascular response to this cold pressor test not because the target organs are less sensitive, but because the sympathetic neural system is less responsive.

These studies on adaptation to cold stimulation show a wide variety of responses of individual resistance to this stress. However, upon repeated exposures the low-resistance individuals may develop, by still obscure mechanisms, a high degree of tolerance. This type of work exemplifies in human beings, in a relatively simple system, a fundamental phenomenon which is essential for a homeostatic equilibrium and for the maintenance of a static

milieu intérieur in spite of variations in the *milieu extérieur*. An unusual environment entails protective exaggerated reactions; however repetition lends a kind of easiness to stress.

REFERENCES

1. Brown, M. and Page, J. The effect of chronic exposure to cold on temperature and blood flow of the hand, J. Appl. Physiol. 5:221 1952.
2. Freeman, N. E. The effect of temperature on the rate of blood flow in normal and in the sympathectomized hand, Am. J. Physiol. 113: 384 1935.
3. Hines, E. A., and Brown, G. E. Standard test for measuring variability of blood pressure, Ann. Int. Med. 7:209 1933.
4. Grant, R. T., Bland, E. F. and Camp, P. D. Observations on the vessels and nerves of the rabbit's ear with special reference to the reaction to cold, Heart 16:69 1932.
5. Coffee, M. A comparative study of young Eskimo and Indian males with acclimatized white males, Third Conference on Cold Injury edited by M. I. Ferrer 1954 Josiah Macy, Jr. Foundation.
6. LeBlanc, J., Hildes, J. and Héroux, O. Tolerance of Gaspé fishermen to cold water, J. Appl. Physiol. 15:1031 1960.
7. Yoshimura, H. and Iida, T. Studies on the reactivity of skin vessels to extreme cold, Jap. J. Physiol. 2:177 1952.

Clinical communications

The significance of prolonged anginal pain (preinfarction angina)

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Prolonged and severe attacks of anginal pain may occur under three circumstances. In some patients the ischemic myocardium may have imposed on it a greater than usual load as by strenuous exertion or severe emotional stress, a hypoglycemic attack, or a sudden elevation of rate or blood pressure as in paroxysmal cardia or paroxysmal hypertension. In a second group the prolonged angina is caused by conditions that are associated with a severe diminution of coronary flow. Examples of such conditions are shock caused by loss of extracellular fluid (hemorrhage, dehydration), massive pulmonary embolism, prolonged and intense tachycardia. In both of these categories removal of the cause of either the increased metabolic demand or of the diminished coronary flow may restore the myocardium to its previous state or, if the ischemia has been sufficiently prolonged and intense, result in the development of a mass of necrotic myocardial tissue.

There is a third and far more common form of prolonged anginal pain that occurs spontaneously, unassociated with a demonstrable cause for increased load or decline in coronary flow. This type is caused by atherosclerotic narrowing of a coronary artery, usually enhanced either by the deposition of thrombus on a roughened intimal lining or by subintimal hemorrhage, or both. It is to this spontaneously occurring form of prolonged anginal pain that this discussion will be limited.

If a patient has an attack of anginal pain which lasts 10 to 15 minutes or longer, and particularly if there has been no obvious provoking cause, it is necessary to determine whether acute myocardial infarction or merely prolonged anginal pain without myocardial necrosis has occurred. The graver forms of myocardial infarction usually present such characteristic features shortly after the onset of the attack that they do not enter into the problem under discussion. It is the milder forms of myocardial infarction that need to be differentiated from the type of ischemic heart disease that by definition is characterized by prolonged anginal pain without evidence of myocardial necrosis. This latter condition has been designated by a number of terms: acute coronary insufficiency, preinfarction angina, impending infarction, the intermediate state, status anginosus. Although no designation thus far proposed is free of objections, the term *preinfarction angina* will be employed throughout this discussion.

Until recently, the diagnosis of preinfarction angina and the separation from acute myocardial infarction were based primarily on failure of new and significant Q waves to develop, and on the absence of such signs of tissue necrosis as fever, leukocytosis, and elevated sedimentation rate.

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Nevertheless differentiation was often difficult for even when infarction was present pathognomonic electrocardiographic findings were often absent or obscured by previous abnormalities such as left bundle branch block or those brought on by former infarctions.

The introduction of the serum transaminase test has provided us with a method of detecting tissue necrosis which is far more accurate and sensitive than any previously available.[1,2] Although the test is not specific for myocardial necrosis, those conditions that are most likely to be confused clinically with acute myocardial infarction are either unassociated with a significant elevation in serum transaminase activity or are accompanied by other features that should lead to the correct diagnosis.[3,4] Generally in the presence of an acute chest pain consistent with that of myocardial ischemia and in the absence of features that strongly point to some other diagnosis, the problem is primarily one of differentiating between preinfarction angina and acute myocardial infarction. For this purpose serial determinations of the serum transaminase activity may usually be regarded as our single most reliable index of myocardial necrosis.

Clinical studies

The following discussion concerns observations made on serum glutamic oxaloacetic transaminase (SGOT) activity in patients who were considered to have preinfarction angina. It is commonly accepted that with this test a level of 40 represents the upper limit of normal and that a peak level is attained within 24 to 48 hours after the onset of the chest pain. Hence when a patient has experienced one or several closely recurrent bouts of chest pain it is common practice to check the level of serum transaminase activity for 2 to 3 days. If the level has not risen above 40 and if there are no other unequivocal signs of infarction the conclusion is usually drawn that the attack falls into the category of preinfarction angina.

Over a period of 5 months, 31 patients presented the classic features of preinfarction angina prolonged anginal pain often recurrent sometimes associated with the appearance of effort angina or with a marked intensification of angina if previously present. Electrocardiograms taken serially revealed no new Q waves although transient S-T-segment and T wave abnormalities were occasionally observed. Serial transaminase tests failed to show figures above 40 during the first 3 days after the patients were hospitalized and during this time there were no other signs of tissue necrosis such as fever leukocytosis or elevated sedimentation rate. Abnormal transaminase levels, however were observed frequently from the fourth day on and occasionally a very brief and mild fever or leukocytosis or increased rate of sedimentation were also witnessed. Since reliance was placed principally on the transaminase test to provide evidence in regard to myocardial necrosis daily leukocyte counts and determinations of the rate of erythrocyte sedimentation were not made and details in regard to these tests are omitted. Because the primary purpose of these observations was to determine the frequency with which the SGOT level became abnormal after the third day 4 patients who had a slight elevation of the transaminase level during the first 3 days after the last attack of pain were not included in this series.

All patients were hospitalized for observation and management as soon as the diagnosis was suspected. They were placed on heparin therapy immediately and dosages were adjusted to give a clotting time of 40 to 60 minutes just before the next injection of heparin. Almost invariably anginal pain subsided within 24 to 36 hours after anticoagulant therapy was instituted and the patients were then encouraged to walk several times a day at a slow pace in the hospital corridors. Transaminase tests[4] were made each day for 7 to 10 days or more after the patients were hospitalized (see Table I).

Table I. SGOT levels in 31 patients with clinical picture of preinfarction angina

Patients with levels over 40 units	23	74%
Patients with levels above 28 units and with maximal variation of 10 units or more	29	93

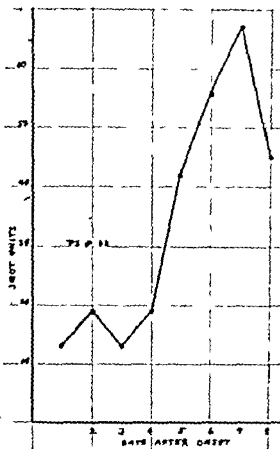


Fig 1. Patient P.S. Daily transaminase tests after an attack of preinfarction angina. The first abnormal figure 42 was observed on the 6th day.

Of the 31 patients 23 (73 per cent) first displayed an SGOT level over 40 units on the fourth to tenth days after the onset of pain or of the last bout of pain (Figs. 1 and 2. Table II). The peak transaminase levels ranged between 41 and 94, most of them were between 41 and 60.

Although 40 units has been generally accepted as the upper limit of normal SGOT activity, there are studies which indicate that this figure is too high and that a more accurate figure is in the vicinity of 28.[2] Moreover there is additional evidence that in normal individuals the maximal variation between the lowest and highest figures obtained over a period of days does not exceed 10 units.[7] This implies that the extent of variation in a series of daily transaminase tests as well as the absolute level of transaminase activity must be considered. For example levels of 13 and 38 in the same patient may have as much significance as a maximal level of 43 in denoting the presence of myocardial necrosis (Table III). When the criterion of a maximal level over 28 units combined with a maximal variation greater than 10 units, was employed, 29 patients (93 per cent) displayed abnormal results indicative of myocardial necrosis.

No special significance is attached to the exact percentages in which abnormal SGOT levels were witnessed. The total number of patients is rather small. The validity of the criterion of SGOT levels greater than 28 and a maximal variation greater than 10 needs to be established by more extended studies. Technical errors may conceivably have accounted for some of the elevations barely above 40 units. Finally, by exclusion of patients who exhibited an elevated transaminase level during the first 3 days some were omitted whose clinical picture was otherwise practically identical with that of those who were included in this series.

When the SGOT peak has been attained it is usual for the transaminase level to fall sharply within the course of a few days and

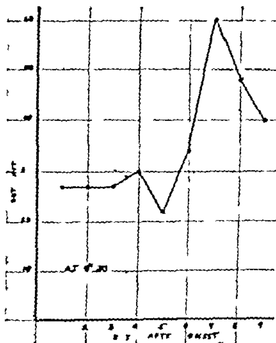


Fig 2. Patient A.J. Daily transaminase tests after an attack of preinfarction angina. The first abnormal figure 60 occurred on the seventh day.

to remain at low levels thereafter. If another rise in SGOT activity occurs, new infarction is suspected. Such secondary rises were observed frequently in this group of patients (Figs. 3 and 4). In no instance was there a corresponding appearance of ischemic pain or of any other clinical or electrocardiographic evidence to indicate a new cardiac injury.

Discussion

The results described above compel a revision of the generally accepted views in regard to the use of the transaminase test in the diagnosis of acute myocardial infarction and a reconsideration of preinfarction angina. It is clear that a peak transaminase level does not necessarily occur during the first 24 to 48 hours after the on-

Table II. *Transaminase levels in 23 patients with preinfarction angina**

Patient	Pain	Days after pain																			
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
A.Je.	—	27	27	27	**50**	22	60	**48**	40												
T.J.	—	19	18	24	13	33	39	46	**53**	41	32	**48**	18	15	20	19	19	24			
A.R.	—	11	11	20	30	34	35	20	41	19	16	22									
A.Jn.	—	6	10	6	14	17	15	**58**	**52**	34	21										
J.F.	—	13	9	9	**53**	17	19	11	35												
M.Wa.	—	12	12	12	38	**91**	**82**	**84**	40	17	34	29	—	—	34	—	**51**	—	30	—	
P.S.	—	13	19	13	19	**42**	**56**	67	45												
E.S.	14	13	13	13	16	33	**45**	37	19	16	11	15	19	15	19	13					
M.S.	**58**	36	17	17	19	26	41	**53**	46	**43**	29	41	16								
H.B.	16	24	19	26	13	20	28	33	28	41	34	**45**	26	30	36	20					
W.M.	21	18	18	36	24	34	28	**45**	**58**	**45**											
M.N.	—	33	20	20	20	31	38	**48**	34	32	38										
T.W.	—	11	13	26	25	**42**	67	60	**45**												
N.T.	—	19	15	19	41	41	18	17	**61**	32	39	26	19								
T.L.	—	25	25	37	34	25	41	34	36	32	23	28	—	—	21						
G.F.	12	17	14	24	28	**54**	41	32	17	17											
T.P.	24	13	24	19	13	34	**48**	**54**	21	17											
L.W.	19	17	28	27	35	32	41	**49**	30	22	17	19									
D.P.	15	18	20	18	**42**	**51**	32	19	13												
B.T.	27	21	14	19	36	**48**	41	17	19	24											
S.R.	22	24	24	28	31	38	**47**	**58**	20	28	17										
E.D.	—	19	19	21	24	**51**	18	19	47	24	21										
F.R.	21	18	17	36	**44**	**46**	**54**	12	18	15											

*Patients in whom the first abnormal SGOT level (above 40) appeared on the fourth day or later after the last attack of anginal pain. Figures over 40 are set in boldface type.

Table III. *Transaminase levels in 6 patients**

Patient	Pain	Days after pain																			
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
E.W.	—	27	20	33	17	14	13	13													
W.Hm.	20	15	12	17	19	19	38	36													
W.B.S.	31	27	15	15	9	19	15	23	26												
A.E.	—	24	20	15	15	—	19	26	25	15	31	12	15	18	15	12					
W.Jn.	—	16	24	17	15	20	22	29	31	29	25										
L.L.	14	13	14	28	34	37	16	19	13												

*Patients in whom the peak SGOT level exceeded 28 units and the maximal variation was greater than [illegible] units. Actually, the peak levels were between 31 and 38 units, and the maximum variation was between 16 and 24 units.

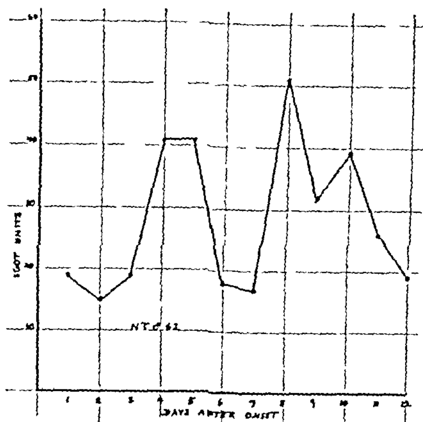


Fig. 3. Patient N. T. Daily transaminase tests after an attack of preinfarction angina. The first abnormal figure, 41, occurred on the fourth day. After a fall to 17, there was a secondary rise to 51 on the eighth day.

set of the attack. In this series in about 75 per cent of the patients who were ordinarily classified as having sustained an attack of preinfarction angina, a transaminase level of over 40 units was first observed on the fourth to tenth days after the attack. If the criterion of a level above 28 combined with a maximal variation greater than 10 units is employed, over 90 per cent of such patients showed evidence of myocardial necrosis. Thus, a high percentage of all patients presumed to have had attacks of preinfarction angina have actually sustained areas of myocardial necrosis sufficiently large to give rise to abnormal levels of transaminase activity. Such an inference is based on the premise that an abnormal transaminase level denotes cellular death. There are observations, however, that demonstrate that ischemia of certain degrees of intensity may injure the cell sufficiently to liberate transaminase without necessarily leading to immediate death. Whether such damaged cells can remain viable and be restored to normal function is not known. Since none of the patients of this series died, it is impossible to know whether abnormal transaminase figures were an expression of cellular death or whether cellular damage without death existed. Consequently, throughout this discussion the use of the term *necrosis* in cases of preinfarction angina is made with the understanding that it may mean histologic cellular necrosis or severe cellular damage short of being lethal to the involved myocardial mass.

Similar observations in regard to increased transaminase levels in preinfarction angina have been described previously.[7] Nydick[8] reported SGOT elevations in about 30 per cent of a group of 50 patients, and about 50 per cent of the abnormal figures occurred after the third day. Employing the criterion of SGOT levels greater than 28 and maximal variations over 10 units in the same person to constitute evidence of myocardial necrosis, Goble and O'Brien[9]

observed abnormal transaminase levels in 50 to 87 per cent of patients who otherwise exhibited all the features of acute coronary insufficiency." But even before the transaminase test had been introduced evidence less decisive but nevertheless highly suggestive had led to the statement "The distinction between the two conditions (myocardial infarction and preinfarction angina) is somewhat artificial because careful study indicates that many patients with typical preinfarction angina reveal clear evidence of necrosis (transient leucocytosis, minimal fever elevation of the sedimentation rate) even though other manifestations of infarction are absent. In such instances one is presumably dealing with a small area of necrosis surrounded by a large zone of ischemia."[29] The present observations with the transaminase test used as a sign of myocardial necrosis fully confirm this view.

What is the significance of these observations which indicate the presence of myocardial necrosis or damage bordering on necrosis in a high percentage of all patients with preinfarction angina? Careful subsequent study of these patients has failed to reveal any detectable diminution of cardiac reserve as manifested by their capacity to perform work loads similar to those undertaken prior to the attack. This is not altogether surprising since the slight elevation of the peak transaminase levels signifies that only a small mass of myocardium has been destroyed or injured. Nevertheless the destruction of so small and clinically insignificant a segment of myocardial tissue should not be construed as evidence that the patient has merely sustained a disagreeable but fortunately benign episode of pain. The fact that in many patients with preinfarction angina a small area of myocardial necrosis may occur means that the anatomic lesion responsible for the obstruction has probably already reduced coronary flow to the involved area to a critical level. Since by Poiseuille's law flow through a tube at a given pressure is proportional to the fourth power of the diameter of the tube, a further and only very slight narrowing of an already critically narrowed blood vessel, as by the deposition of a small amount of additional thrombus could bring about so serious a reduction in blood flow as to cause frank infarction.

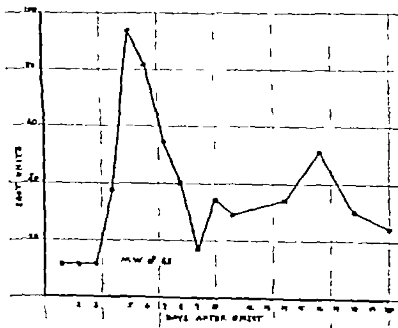


Fig. 4. Patient M. W. Daily transaminase test after an attack of preinfarction angina. The first abnormal figure, 94, occurred on the fifth day. After a fall to 17 on the ninth day a secondary rise to 51 occurred on the fifteenth day.

Obviously such a diminution in coronary flow could take place either in the coronary artery primarily responsible for blood flow to the affected myocardium or in a coronary vessel supplying important collaterals to this area.

In this series, the ischemia responsible for the attack of preinfarction angina resulted in a delayed rise with peak levels lower than those usually witnessed in frank infarction and the occasional occurrence of the secondary rise in SGOT. Why should the transaminase peak appear as late as 5 to 10 days after the attack of preinfarction angina when it appears almost invariably within 24 to 72 hours after frank infarction. One explanation could be that no transaminase elevation resulted from the ischemia responsible for the preinfarctional pain but that after a variable number of days a painless exacerbation of the ischemia caused the delayed increase in transaminase. A *painless intensification of* the ischemia occurring in each of the patients with a delayed rise seems to be a gratuitous assumption particularly since there were no other clinical phenomena to indicate a worsening of the patient's condition. A more probable explanation for the delayed rise would be that the intensity of the ischemia in preinfarction angina was sufficient to cause severe damage in a small mass of myocardium but insufficient to cause prompt cellular death. Only after a number of days did cellular disintegration reach that level which is associated with the liberation of transaminase.

Essentially the same explanation may be invoked to account for the secondary rise in transaminase. During the attack of preinfarction angina the involved myocardium is comprised of confluent areas which are variously affected by the ischemia, depending primarily on variations in the richness of collateral blood flow. The foci of necrosis must be small to account for the low peak of transaminase levels. Moreover more than one focus of necrosis may be present in the same mass of ischemic myocardium. Thus, one small area may have been subjected to an intensity of ischemia sufficient to cause cellular death and disorganization responsible for a peak of 41 on the fourth day. Another slightly larger area may have been destroyed but by a somewhat less intense ischemia so that cellular disorganization with liberation of transaminase to a level of 51 does not take place until the eighth day (Fig. 3). The rest of the ischemic myocardium remains viable although some portions of it must have barely escaped necrosis.

These interpretations of the behavior of the transaminase test after an attack of preinfarction angina are supported by histologic studies that show within the same ischemic myocardium all stages of death and healing from earliest necrosis to early fibrosis.[5-17]

It seems clear that the basic difference in the behavior of the transaminase after frank infarction and that after preinfarction angina is simply one of intensity of ischemia. In the former the severity of the ischemia is such as to cause immediate and fairly uniform necrosis of a *macroscopic* mass of myocardium with prompt libera*tion of transaminase. In the latter* the ischemia suffices only to cause variable degrees of cellular injury. Only small and possibly microscopic patches of necrosis appear, cellular death and disorganization proceeding more slowly and at different rates.

The potentially serious nature of an attack of preinfarction angina rests on more than theoretical considerations. Although there are some writers who regard anticoagulant therapy as either unnecessary or a matter of little urgency there are others whose reports indicate that 25 to 93 per cent of patients with preinfarction angina develop frank and serious infarction within 4 to 12 weeks after the onset of the attack if anticoagulant therapy is not used. On the other hand frank infarction is reduced to 3 to 10 per cent during the same period of time if anticoagulants are given for at least 6 weeks.[13, 14] All of the patients in the present series were given anticoagulants for 5 or more months after the attack. In only one did frank infarction develop during this time.

Although the value of anticoagulant therapy as judged by the above figures, appears to be convincing one must bear in mind the possibility that it may actually be less effective than it seems to be. Anticoagulant therapy could have value only if a thrombus were responsible for the ex

acerbation of myocardial ischemia. However the latter may also be caused by progressive atherosclerotic narrowing with or without subintimal hemorrhage but without formation of thrombi. Consequently in an undetermined but small percentage of patients in this and other series reported upon in the literature, anticoagulant therapy could have played no significant role in preventing frank infarction.

Moreover there is abundant evidence that patients suffering from myocardial ischemia are not immune to the placebo influence of otherwise ineffective forms of therapy.[16] It is possible therefore that management of the patient including anticoagulant therapy may have done nothing more than reassure an anxious patient. The resultant diminution in heart rate and in the endogenous formation of excessive quantities of catecholamines[17] could conceivably reduce myocardial oxygen requirement enough to prevent frank infarction. This possibility could be answered only by a well-controlled double-blind study.

Despite these considerations and until there is unequivocal evidence that anticoagulant therapy is ineffective the management of the patient with preinfarction angina should be based on an appreciation of the fact that blood flow to the affected myocardium has already been reduced to a critical level. Although one can never be certain that thrombotic occlusion is present, this type of lesion is present in so high a percentage of patients that one is justified in administering anticoagulant therapy promptly and continuing it for 6 weeks or longer. Physical activity should be sharply restricted for at least 2 to 3 weeks. The purpose of this regimen is to reduce the metabolic needs of the heart to prevent further narrowing of the coronary lumen by formation of thrombi and to afford time for the development of collaterals sufficient to increase blood flow to the affected area above its presently precarious level.

It is evident that there should be no sharp distinction between preinfarction angina and frank infarction. All ischemic heart disease should be considered to be a continuous spectrum of increasing severity of ischemia, ranging from the mildest angina of effort without necrosis to the most massive infarction. In a high percentage of patients with preinfarction angina evidences of necrosis can be detected and the more severe forms of preinfarction angina merge insensibly with the milder forms of frank infarction. Regardless of the terminology one prefers—preinfarction angina, coronary insufficiency, impending infarction, status anginosus, or the intermediate state—it is important to recognize that necrosis has already occurred in many and that far more serious infarction is likely to develop if appropriate therapy is not instituted promptly.

Summary and conclusion

Necrosis of the myocardium takes place in a high percentage of all persons who have spontaneous attacks of preinfarction angina. Abnormal transaminase levels may first appear on the fourth to tenth days after the attack and not during the first 2 days as is now generally considered to be the case. A secondary rise in transaminase may not be the result of a new occlusion or the propagation of the original thrombus. It may be caused only by the slow and uneven death and disorganization of small areas of myocardium subsequent to the original attack of ischemia. The importance of spontaneous preinfarction angina comes from the fact that diminution in blood flow to an area of the myocardium has already reached a critical and dangerously low level, and appropriate measures, primarily anticoagulant therapy and restriction of activity should be instituted promptly to prevent so far as possible the development of a larger and more serious frank infarction.

REFERENCES

1. Agress, C. M. Evaluation of transaminase test. Am. J. Cardiol. 3:74, 1959.
2. Hamolsky, M. W., and Kaplan, N. O. Measurements of enzymes in the diagnosis of acute myocardial infarction, Circulation 23:102, 1961.
3a. Resnik, W. H., and Harrison, T. R. *In* Harrison, T. R., editor: Principles of internal medicine, ed. 3, New York, 1958, McGraw-Hill Book Company, p. 43.
3b. Ibid., p. 1264.
4. Reitman, S., and Frankel, S. A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminase, Am. J. Clin. Path. 28:56, 1957.
5. Dewar, H. A., Rowell, N. R., and Smith, A. J. Serum glutamic oxalacetic transaminase

acute myocardial infarction, Brit. M. J. 2:1121 1958.

6. Goble, A. J. and O'Brien, E. N. Acute myocardial ischemia: significance of plasma transaminase activity. Lancet 2:373 1958.

Russell, N. R. and Smith, A. J. Multiple serial enzyme studies in acute myocardial infarction. Brit. M. J. 2:459 1959

8. Nydick, I. Ruegsegger, P. Wroblewski, F. and LaDue, J. S. Variations in serum glutamic oxalacetic transaminase activity in experimental and clinical coronary insufficiency, pericarditis and pulmonary infarction. Circulation 15:3 4 1957

9. Horn, H. Field, L. E. Dack, S. and Master, A. M. Acute coronary insufficiency: pathological and physiological aspects. Am. HEART J 40:63 1950

10. Mounsey, P. Prodromal symptoms in myocardial infarction. Brit. Heart J. 13:215 1951

11. Schlesinger, M. J. and Reiner, L. Focal myocytolyses of heart. Am. J. Path. 31:443 1955

12. Halderstleben, D. Value of T-wave abnormalities in the diagnosis, prognosis, and treatment of coronary arteriosclerotic heart disease. M. Ann. District of Columbia 28:477 1959

13. Wood, P. Acute and subacute coronary insufficiency. Brit. M. J. 1 1779 1961

14. Nichol, E. S., Phillips, W. C., and Casten, G. G. Virtue of prompt anticoagulant therapy in impending myocardial infarction: experiences with 318 patients during a 10 year period, Ann. Int. Med. 50:1158 1959

15. Beamish, R. E., and Storrie, V. M. Impending myocardial infarction. Recognition and management, Circulation 21:1107 1960

16. Beecher, H. K. Surgery as placebo. A quantitative study of bias, *J.A.M.A. 1 6 1102, 1961*

1. Elmadjian, F., Hope, J. M. and Lamson, E. T. Excretion of epinephrine and norepinephrine in various emotional states, J. Clin. Endocrinol. 1 :608 1957

Premature ventricular beats in complete A V dissociation The returning cycle

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Premature ventricular contractions in slow idioventricular rhythm are of interest because of the various ways such early beats can influence the dominant rhythm. Extensive experimental investigation early in the pre-electrocardiographic era[1-7] revealed that the ventricular interval that follows a premature contraction—*the returning cycle*[8]—did not always equal the original automatic cycle but was frequently longer and occasionally shorter. A prolongation could be explained readily either by taking into account the time required for propagation of the premature impulse to the dominant center or by a transient depression of the latter by its early extraneous discharge[6,7] But shortening of the returning cycle was difficult to understand and has remained unexplained.

In clinical electrocardiograms premature ventricular beats are commonly found when complete A V dissociation is the result of an advanced A V block. The length of the returning cycle after the premature beats in such cases is as unpredictable as in the experimental model. According to previous statements it usually equals, or may be longer than the dominant cycle[9-12] but a reduction has sometimes been noted[11,12] or illustrated.[14] Both prolongation and shortening have been observed on occasion in the same case[12, Obs. 14].

The paucity and inconsistency of available data prompted us to investigate the problem in our own material and to attempt to clarify and to classify the different mechanisms that conceivably may come into operation.

Material and methods

Electrocardiograms of 120 cases in which A V dissociation was the result of advanced A V block[14] were reviewed for the occurrence of premature beats. In 50 the ventricular action was regular throughout the entire observation. In 21 a ventricular irregularity was noted attributable to (1) an uneven slow discharge of a single ventricular pacemaker (2) a temporary exit block of the idioventricular impulses[14] or (3) capture of the ventricles by supraventricular impulses. Premature ectopic ventricular beats ("extrasystoles") as the principal cause of the ventricular irregularity could be established in 39 cases. Of these, 13 had to be excluded as *unsuitable* for the purposes of the study because of persistent ventricular bigeminy brevity of

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Fig. 1. Ventricular premature systoles in complete A-V dissociation due to an advanced A-V block. The three records are from different patients. The returning cycle (*RC*) after the premature beat in *B* is precisely as long as that of the regular dominant rhythm; in *A* it is 0.10 second longer and in *C* it is 0.14 second shorter.

the periods recorded, and other technical inadequacies. Thus, records of 26 patients were available for further analysis.

The *interpretation of the mechanisms* that determine the duration of the returning cycle after a premature beat was based on the following considerations: (a) stability or variability of the dominant ventricular pacemaker gauged by rate, contour, and QRS duration of consecutive *slow ventricular beats*; (b) *similarity or* difference in the shape of dominant and premature beats; and (c) the time relationships of dominant (pacemaker) and premature ("ectopic") impulses.

Results

Fig. 1 illustrates that the length of the returning cycle subsequent to a premature *ventricular complex in complete A-V dissociation* with a slow and regular ventricular pacemaker may exceed that of the basic rhythm (*A*), equal it (*B*), or be considerably shorter (*C*). The incidence of these three possible events in the material studied is summarized in Table I.

In 14 instances the measurements were consistent in all available records of a given case. In 12, shorter as well as longer or unaltered postectopic cycles were encountered in long records or on different occasions. Among the 14 cases in which there were consistent measurements the three types of returning cycle occurred with about the same frequency. When the *over-all incidence was considered in all* 26 cases regardless of consistency, there were 10 in which the returning cycle at one time or another exceeded the dominant one, 15 in which it was found to be equal to, and 16 in which it was sometimes shortened in comparison to the dominant cycle.

The mechanisms responsible for this variability of the returning cycle proved to be manifold and sometimes several of them had to be inferred in a given single case. The material could be divided into two groups. Group I included cases in

Table I. The returning cycle after ventricular premature systoles in 26 cases of A-V dissociation due to advanced A-V block

Returning cycle	Number of cases
Consistently prolonged	4
Consistently unaltered	5
Consistently shortened	5
Variable	12
Total	26

which there was irregularity of the dominant rhythm due either to the uneven discharge of a single pacemaker or to two or more pacemakers succeeding each other in the longer stretches of the records or competing for control of the ventricles. Group II comprised all of those cases in which the premature beats interrupted the action of a single ventricular pacemaker which *was discharging at a constant rate* with no more than 0 04 second difference in the length of successive cycles.

Most of the cases in which the length of the returning cycle varied from one premature beat to the other were found in Group I Obviously in the absence of a steady dominant rhythm the length of the cycle which follows a premature beat is determined by chance depending on whether the extra beat occurs during a *period of quickening or slowing of the* dominant impulses. Yet in some of these cases a change in the basic rhythm and in the location of the pacemaker appeared to be induced by and dependent on the occurrence of a single premature contraction (Fig 2) and then the first cycle of the new rhythm was always shorter than the ensuing ones. In these latter instances a stimulating effect of the premature beat upon latent potential pacemaker centers had to be postulated [9] There was no case in which a change in the origin of the pacemaker was preceded by a prolongation of the returning cycle attributable to a transient inhibition (depression) of the dominant center by the early extraneous impulse.[17]

In Group II cases with a persistent and regular single dominant pacemaker of the ventricles, the duration of the returning cycle after a premature beat was found to be determined by three interrelated factors (a) remoteness or proximity of the centers releasing the dominant and premature impulses (b) the timing of the premature impulse within the dominant cycle—the coupling interval and (c) the possibility and speed of propagation of the premature impulse to the site of the dominant pacemaker Evidently the earlier the premature beat occurs after a dominant one and the farther away its origin is, the longer will be its conduction time through the ventricular myocardium and to the pacemaker On the basis of these principles five mechanisms can result. Two of these will augment the returning cycle, two will reduce it and one will leave it unaltered Details of these five mechanisms are presented diagrammatically in Fig 3 and are summarized below

1 The returning cycle will *lengthen* (a) when the premature impulse takes its origin in an area remote from the pacemaker *when it occurs early in the cycle of the* latter and when its rate of propagation to the pacemaker site is normal or delayed

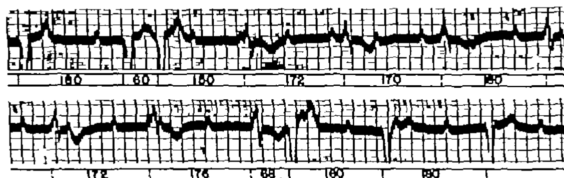


Fig 2 Ventricular premature beats in A-V block with complete A-V dissociation and an unstable idioventricular pacemaker Continuous *Lead II* the last beat of the upper strip is reproduced as the first beat of the lower strip. The numbers in the diagrams to this and all subsequent figures represent hundredths of a second. Two slow idioventricular pacemakers with irregular discharge corresponding to rates of 33 to 40 dominate the ventricles The switch from one pacemaker to the other is induced by ventricular premature systoles which resemble one of the two pacemakers in contour The returning cycle after these premature beats is shorter than any of the idioventricular cycles. Discussed in text

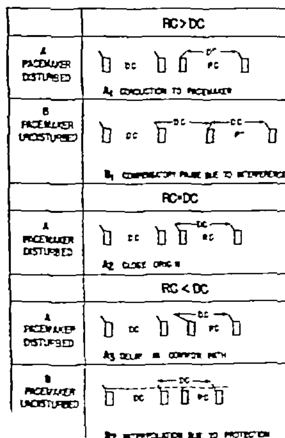


Fig. 3. Diagrammatic representation of the mechanisms which determine the length of the returning cycle after a premature ectopic ventricular systole in an otherwise regular idioventricular rhythm. Examples of mechanisms A_1 are illustrated in Figs. 1,A and 5; of mechanism A_2 in Figs. 1,B and 4,B; of mechanism A_3 in Figs. 1,C and 6; of mechanism B_1 in Fig. 4,A; and of mechanism B_2 in Fig. 5. Discussed in text.

(mechanism A_1) and (b) when the premature impulse occurs so late in the dominant cycle that the two impulses meet and interfere with each other—the returning cycle then becomes fully compensatory (mechanism B_1).

2. The returning cycle will *shorten* (a) when pacemaker and premature impulse share a common path and direction of propagation through the myocardium, at least in part, and when conduction of the premature impulse—in this common path—*is slower than conduction of impulses* arising in the pacemaker (mechanism A_3) and (b) when the pacemaker region is shielded from the extraneous (premature) impulse by a region of unidirectional conductivity[18]—the premature beat being interpolated (*mechanism B_2*).

3. The returning cycle will *equal* the dominant one when the premature impulse originates in close proximity to the pacemaker or within the pacemaker region itself and the two impulses are propagated through the myocardium at equal speeds (mechanism A_2).

Comment

One could expect that premature beats of automatically beating ventricles might influence the dominant rhythm in the same manner as atrial premature systoles affect the normal sinus rhythm. Under both circumstances ectopic and pacemaker impulses originate in the same set of chambers, and hence the interrelated factors noted above that determine the effect of the premature beat upon the dominant rhythm should come into action with comparable frequency and consequences. The present study revealed that this analogy is not complete in several aspects, as will be discussed below.

Incidence of the various types of returning cycles. It is a well-established fact[19,21] that after an atrial premature beat the sinus interval is prolonged as a rule, less commonly it maintains its original length. It may appear shortened when the sinus node discharges irregularly, but hardly ever in the presence of a regular rhythm. Contrariwise, in the ventricular variety of a comparable arrhythmia, we frequently encountered shortening of the returning cycle after a premature beat (Table I) and this occurred even when the ventricular pacemaker was perfectly regular (Figs. 1,C and 6).

Mechanisms determining the length of the returning cycle.

A. PROLONGATION OR EQUALITY. The pause after an atrial premature systole, that is, the prolonged returning cycle, may or may not be fully compensatory, depending on whether the ectopic impulse reaches the site of the dominant pacemaker ahead of or *after its spontaneous discharge*.[9,10,21,23] The pause may become longer than compensatory when the extraneous premature discharge causes a transient inhibition of the pacemaker

activity[17] and this in turn frequently induces a transient shift in the location of the pacemaker.[8] The likelihood of encountering one or the other of these possibilities in a clinical electrocardiogram is about equal in the case of atrial premature systoles, but this is not true in the case of ventricular premature beats disturbing an idioventricular rhythm. If the idioventricular rhythm is regular (Group II) the findings of a truly compensatory pause is extremely rare. Obviously, for mechanism B_1 of Fig. 3 to come into operation, ectopic and dominant impulses must discharge in close succession. The chances for this to occur are good with atrial premature systoles during a normal or accelerated sinus rhythm, but poor in slow idioventricular rhythms—unless the coupling of the premature ventricular beats happens to be unusually long, as was the case in our Fig. 4,*A*. We have not found a similar case illustrated in the literature.

The analogy between atrial and ventricular premature beats is likewise in complete in our Group I (cases with an irregular or changing basic rhythm). When a single irregular pacemaker is permanently in action, the length of the returning cycle after a premature beat remains a matter of chance in the atria, as well as in the ventricles. However, when the location of the pacemaker shifted in the wake of the premature beat, as is frequently the case, the first cycle of the new rhythm was found to be shortened in the ventricle (Fig. 2) rather than lengthened as usually happens in the atrial variety. The reasons for this disparity are not obvious and can only be inferred. It would appear that in the ventricles the physiologic transient inhibition of the dominant pacemaker activity *subsequent to an extrinsic premature discharge* may be associated with and obscured by a simultaneous enhancing action of the premature impulse upon latent impulse generation in other potential pacemaker centers.

B. SHORTENING. When the premature beat occurs *in an otherwise perfectly regular rhythm*, one of two mechanisms (A_3 and B_3 in Fig. 3) can account for a reduction of the returning cycle. Interpolation of a homologous premature beat (mechanism B_3) requires the implication of protection of the pacemaker area from invasion by the ectopic impulse. Such an event appears to be very rare, and only a few unquestionable cases are on record in which this occurred in the atria[9,16,22,23] or ventricles.[9,22,23] Two instances were found in the present series, and one is illustrated in Fig. 5.

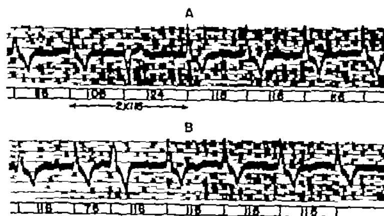


Fig. 4. Premature beats of different origin in complete A-V dissociation due to an advanced A-V block. The two strips are portions of a long Lead III. I. *A*, the premature beat differs considerably from the dominant beats, has a long coupling interval, and the returning cycle corresponds to a compensatory pause (cf. mechanism B_1 in Fig. 3). In *B* the premature beat resembles the dominant beat and the returning cycle equals the dominant one (mechanism A_1 in Fig. 3).

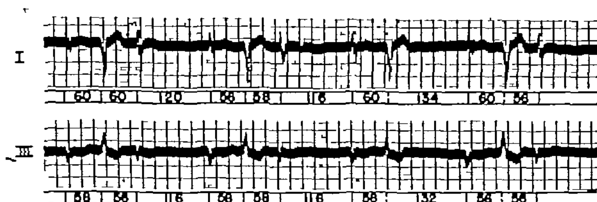


Fig 5 Interpolated ventricular premature systoles during complete A V dissociation (in atrial fibrillation). The premature (ectopic) beats differ from the regular idioventricular ones by having their QRS and T deflections oppositely directed. The first, second, and last premature beats in each lead do not disturb the regular discharge of the idioventricular pacemaker (cf mechanism B_1 in Fig 3); the third premature beat is followed by a prolonged idioventricular cycle (cf mechanism A in Fig 3). This indicates that the protection mechanism which shields the pacemaker from ectopic impulses is not permanently in action and also rules against an alternative interpretation, ie, an intermittent 2 1 exit block of a rapid continuous idioventricular rhythm (with a cycle length of *0.56* to *0.58* second)

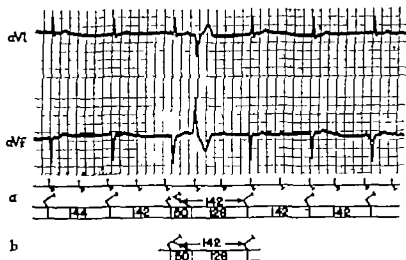


Fig 6 A supraventricular premature systole with aberrant ventricular conduction in A V block with *complete* A V *dissociation recorded simultaneously* in two leads. The manifest returning cycle (*128*) after the premature beat is 0.14 second shorter than the regular automatic cycle (*142*), which corresponds to mechanism A_2 in Fig 3. Diagrams *a* and *b* indicate two possible alternative interpretations. Discussed in text

However in the majority of such cases the strict criteria[9] that have to be postulated to establish interpolation do not apply and hence one must infer that the other mechanism is in operation viz retardation of the premature impulse in a propagation path which it shares partly or completely with impulses coming from the dominant pacemaker.[12] This mechanism (A_2 in Fig 3) in which the reduction of the returning cycle is only apparent is well known to take place in A V nodal rhythm either in the presence of incomplete A V dissociation subsequent to a

ventricular capture[1,21,31] or in the presence *of retrograde conduction subsequent* to a reciprocal beat.[16,22,28,29] In complete A-V dissociation this principle can be applied most readily when close similarity of the electrocardiographic contour of premature and dominant beats indicates both a similar site of origin and a similarity in the mode of ventricular propagation of the two types of impulses. However a difference in contour even when considerable as in our Figs. 1 *C* and 6 does not of necessity exclude this mechanism since aberrant ventricular conduction is prone to occur in early beats, particularly when the basic rhythm is slow and as a consequence, the refractory phase of ventricular conducting tissues is longer than usual.[22] The intriguing problem may then arise whether to locate the site of the common path, and with it the origin of premature and automatic beats, in regions proximal or distal to the bifurcation of the common bundle.

The bearing of a shortened returning cycle upon the origin and mechanism of premature beats in A-V dissociation. Hering[3] in 1905 expressed the idea that in automatically beating ventricles the length of a postextrasystolic interval may depend on the location of the automatic center, e.g., in the "connecting fibers" rather than within

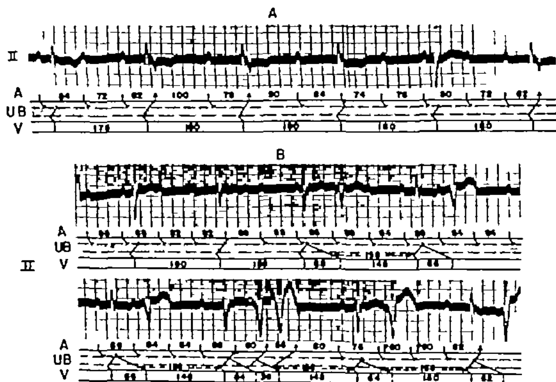


Fig. 7. Unidirectional A-V block with incomplete A-V dissociation (and atrial captures) in which single and pairs of ventricular premature beats are attributable to re-entry within the A-V junction. Record *A* illustrates the basic mechanism. A region of unidirectional block in the A-V junction (stippled area in the diagram) stops all sinus impulses, but can be traversed by the retrograde impulses of the slow and regular ventricular pacemaker. When appropriately timed after a sinus impulse, the retrograde impulse reaches and activates the atria (atrial capture—cf. fourth, sixth, and last P waves). Record *B* was obtained in the same patient several da[illegible] later. The two strips are continuous; the last two ventricular beats of the upper strip are reproduced as the first two beats of the lower strip. The same mechanisms are in operation as in record *A*, but the regularity of the ventricular rhythm is disturbed by premature beats of bizarre appearance. Note that the manifest returning cycles after the premature beats are invariably shorter (by 0.08 to 0.12 second) than the automatic cycle and also that retrograde activation of the atria, [illegible] prolonged conduction time [illegible] induced by the pair of premature beats in the middle of the lower strip. Discussed in text.

the ordinary ventricular myocardium This problem becomes even more involved when the origin and mechanism of the premature beat, as well as the site of the pacemaker are under question Two such examples are illustrated in Figs. 6 and 7

In Fig 6 the bizarre configuration of the premature beat contrasts sharply with the almost normal contour of the automatic beats. This latter fact and the rate of the basic rhythm suggest that the pacemaker impulses originate somewhere between the blocked region of the A V junction and the bifurcation of the common A V bundle The shortened cycle after the premature beat in the presence of otherwise perfectly regular pacemaker impulses, indicates that the mechanism of a common path (A_1 in Fig 3) is in operation Hence, the premature impulse too may arise in A V junctional tissues and be aberrantly conducted in the ventricles. If this is true then the premature beat could have been caused by one of two mechanisms as indicated in the two diagrams either a sporadic early [illegible] e of a second junctional pacemaker *(a)* or re-entry of the pacemaker impulse within the A V junction *(b)* induced by its slow and concealed retrograde penetration into more proximal portions of the A V junction[illegible]

Although there is no way to prove—or to disprove—the partial retrograde propagation of the pacemaker impulse in Fig 6 the feasibility of such an event is well demonstrated in Fig 7 a case of unidirectional block with incomplete A V dissociation and atrial captures. The complex mechanism of this type of conduction disorder has been outlined elsewhere[illegible] and is indicated in the diagram. In record *A* the perfectly regular sequence of the ventricular beats suggests that their variable contour is caused by differences of intraventricular spread of impulses generated in a *single* pacemaker the location of which however above or below the bifurcation is uncertain from this record.

The same two types of ventricular complexes, at a slightly faster rate, are seen in record *B* but their regular sequence is now disturbed by single and a pair of premature beats with markedly prolonged QRS complexes and a reduced returning cycle. Retrograde activation of the atria with prolonged R P intervals by the dominant pacemaker as well as by the premature impulses takes place whenever the timing of the sinus impulses permits it.[illegible] Thus in this case two conditions are fulfilled which make it possible to attribute the premature beats to a re-entry process within the A V junction namely (a) the actual demonstration of a slow retrograde spread of impulses through the A V junction and (b) retardation of the premature impulse in a stretch of pathway which it must share during propagation to the ventricles with impulses coming from the pacemaker (mechanism A_1 of Fig 3)

Detailed analysis of special cases as exemplified in Figs. 6 and 7 has some implications with regard to the controversial theories of coupled premature beats (extrasystoles)[illegible] Such findings lend support to the concept of re-entry[illegible] as well as to the notion that many premature beats which are considered by the usual criteria to be ventricular may actually originate at supraventricular levels.[illegible] However the results of our study do not justify any general conclusion. Mechanisms outlined in Fig 3 may conceivably be in action regardless of whether the premature beat is ascribed to a repetitive response to the pacemaker impulse[illegible] or to its re-entry into the ventricles On the other hand equal difficulties are encountered in ascribing the premature beats to one or the other mechanism when account has to be taken of the long coupling interval responsible for a truly compensatory pause in a slow ventricular rhythm (mechanism B_1 in Fig 3) *At present it would appear that equal* validity must be given to both of the principal theories and that one or the other may be better suited to explain conditions in a particular case In fact, the concept of re-entry and repetitive response are not mutually exclusive and it seems that one may initiate the other Such a link between the two mechanisms—which may exist particularly during the "vulnerable phase" of the cycle—appears to be the background[illegible] of another practically important, aspect of premature beats during slow idioventricular rhythms that is their tendency to multiplication. This will be the subject of a subsequent study

Conclusions and summary

1. Premature ventricular beats during a slow idioventricular rhythm are followed by an interval that may be equal to, longer than, or shorter than the cycle of the dominant beats. In a review of 26 such cases, shortening of the returning cycle after a premature beat was found to occur with unexpected frequency.

2. The variability of the returning cycle is caused by a number of circumstances. When the ventricular pacemaker is unstable the length of the returning cycle becomes a matter of chance. With a single steady pacemaker it is determined by three interrelated factors: (a) the distance of the "ectopic" center from the pacemaker, (b) the timing of the premature impulse within the dominant cycle, and (c) the speed (and possibility) of propagation of the premature impulse to the pacemaker area.

3. Reduction of the returning cycle in the presence of a regularly discharging pacemaker can, in the majority of cases, be ascribed to a delay in the propagation of premature impulses in a pathway shared in common with the dominant impulses. Exceptionally, it may be caused by interpolation of the premature beat.

4. Ventricular premature systoles of automatically beating ventricles cannot be likened in every respect to atrial premature systoles during sinus rhythm. The latter tend to depress the pacemaker, whereas ventricular premature beats sometimes appear to exert a stimulating effect on pacemaker activity in the ventricles, leading to shortening of the returning cycle. A shortening of the returning cycle is hardly ever encountered subsequent to an atrial premature contraction. A fully compensatory pause, on the other hand, although common in the atrial variety, is extremely rare in the ventricular variety.

5. Premature ventricular beats with a shortened returning cycle, even when bizarre in shape, may be caused by a reentry mechanism in the A-V junction. This seems to be especially the case when the automatic beating of the ventricles is the result of a unidirectional A-V block with incomplete A-V dissociation and atrial captures.

REFERENCES

1. Cushny, A. R., and Matthews, S. A.: On the effects of electrical stimulation of the mammalian heart, J. Physiol. 21:213, 1897.
2. Woodworth, R. S.: Maximal contraction, "staircase" contraction, refractory period and compensatory pause of the heart, Am. J. Physiol. 8:214, 1903.
3. Hering, H. E.: Nachweis der Automatie der (mit den Vorhöfen oder Vorhofresten in Verbindung stehenden) Kammern bzw. Verbindungsfasern des Säugetierherzens durch Auslösung ventrikulärer Extrasystolen, Pflügers Arch. ges. Physiol. 107:108, 1905.
4. Erlanger, J., and Blackmann, J. R.: Further studies on the physiology of heart block in mammals. Chronic auriculoventricular heart block in the dog, Heart 1:177, 1909-1910.
5. Hofmann, F. B., and Holzinger, J.: Über den Einfluss der Extrasystolen auf die Rhythmik spontan schlagender Herzteile, Ztschr. Biol. 57:309, 1912.
6. Cushny, A. R.: Stimulation of the isolated ventricle, with special reference to the development of spontaneous rhythm, Heart 3:257, 1912.
7. Rothberger, C. J., and Winterberg, H.: Über Extrasystolen mit kompensatorischer Pause bei Kammerautomatie und über die Hemmungswirkung der Extrasystolen, Pflügers Arch. ges. Physiol. 146:385, 1912.
8. Lewis, T.: The mechanism and graphic registration of the heart beat, ed. 3, London, 1925, Shaw and Sons.
9. Scherf, D., and Schott, A.: Extrasystoles and allied disorders, N. Y., 1953, Grune & Stratton.
10. Katz, L. N., and Pick, A.: Clinical electrocardiography. Part I. The arrhythmias, Philadelphia, 1956, Lea & Febiger.
11. Lichtheim, K.: Über einen Fall von Adams-Stokesscher Krankheit mit Dissociation von Vorhof- und Kammerrhythmus, Deutsches Arch. klin. Med. 85:360, 1906.
12. Naish, A. E.: Premature ventricular beats in heart block, Quart. J. Med. 6:196, 1912-13.
13. Frey, W.: Klinische Beobachtungen über Arrhythmie der automatisch tätigen Ventrikel, Deutsches Arch. klin. Med. 119:437, 1916.
14. Scherf, D.: Retrograde conduction in complete heart block, Dis. Chest 35:320, 1959.
15. Spang, K.: Rhythmusstörungen des Herzens, Stuttgart, 1957, Georg Thieme.
16. Pick, A., and Langendorf, R.: Exit block of cardiac pacemakers. Abstract, Scientific Sessions of the American Heart Association, Bal Harbour, Fla., October, 1961.
17. Pick, A., Langendorf, R., and Katz, L. N.: Depression of cardiac pacemakers by premature impulses, Am. Heart J. 41:49, 1951.
18. Schott, A., and Scherf, D.: Further observations on coupled extrasystoles and automatic ventricular rhythms, Brit. Heart J. 21:177, 1959.
19. Wenckebach, K. F., and Winterberg, H.: Die Unregelmässige Herztätigkeit, Leipzig, 1927, W. Engelmann.
20. Winternitz, M.: Zur Analyse seltener Leitungsstörungen im Menschenherzen, Wien. Arch. inn. Med. 22:445, 1932.

21. Langendorf, R., Lesser, M. E., Plotkin, P., and Levin, B. D.: Atrial parasystole with interpolation: its bearing on the concept of sinoatrial block. Abstract, Scientific Sessions of the American Heart Association, Bal Harbour, Fla., October 1961.
22. Weser, E.: Interpolierte Extrasystolen bei Kammerautomatie, Deutsches Arch. klin. Med. 140:73, 19__.
23. Holzmann, M.: Die Rhythmusstörungen des Herzens, *In* Handbuch der inneren Medizin, Vol. 9, Part II, p. 36, Berlin, 1960, Springer Verlag.
24. Scherf, D.: Reizleitungsstörungen im Bündel. III. Mitt. Nachweis einer Leitungsstörung im Bündel and klinischen Fällen, Wien. Arch. inn. Med. 12:37, 1926.
25. Pick, A., and Langendorf, R.: A case of reciprocal beating with evidence of repetitive and blocked re-entry of the cardiac impulse, Am. Heart J. 40:13, 1950.
26. Fleischmann, P.: The latent and manifest reciprocation mechanism in lower atrioventricular nodal rhythm coexistent with sinoventricular rhythm, Acta cardiol. 6:163, 1951.
27. Hoffman, B. F., and Cranefield, P. F.: Electrophysiology of the heart, New York, 1960, McGraw-Hill Book Company, Inc.
28. Kistin, A. D.: Mechanisms determining reciprocal rhythm initiated by ventricular premature systoles. Multiple pathways of conduction, Am. J. Cardiol. 3:365, 1959.
29. Dohi, I., Dohi, Y., Tada, T., Mita, Y., Yoshida, K., Matsuura, Y., Maruyama, R., Koyama, G., and Taketani, T.: Experimental studies upon reciprocal rhythm, Jap. Heart J. 1:275, 1960.
30. Langendorf, R., and Pick, A.: Approach to the interpretation of complex arrhythmias, Prog. Cardiovas. Dis. 2:706, 1959.
31. Scherf, D., and Schott, A.: Mechanism of origin of ectopic beats. A hypothesis, with special reference to extrasystoles, Am. J. Cardiol. 3:351, 1959.
32. Bisteni, A., Sodi-Pallares, D., Medrano, G. A., and Pileggi, F.: A new approach for the recognition of ventricular premature beats, Am. J. Cardiol. 5:358, 1960.

Clinical evaluation of guanethidine sulfate, a new antihypertensive agent

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Normalization of elevated blood pressure has been shown to increase the longevity and to decrease the morbidity of hypertensive patients. To accomplish this a wide variety of compounds has been introduced in recent years. Unfortunately none of these has been universally effective and each has had its limitations, such as unpleasant side effects, toxicity, development of tolerance, etc. Hence the continuing search for new medications has resulted in the introduction of guanethidine sulfate,† a potent hypotensive agent which experimentally produces blockade at the postganglionic sympathetic nerve terminals without parasympathetic effect.[1] Recently published clinical studies[2-4] have reported the drug to be very potent and free from the parasympathetic side effects which have characterized drugs that produce ganglionic blockade. This study of the medication was undertaken for the following reasons: (1) to compare the hypotensive potency and side effects of guanethidine with trimethidinium, (2) to determine the feasibility of transferring patients from a ganglionic blocker to guanethidine, (3) to decide the need for ancillary medications in attaining and maintaining control of the blood pressure with guanethidine, and (4) to test the usefulness of the drug in the management of mild and moderate hypertension. The study was designed to be of sufficient duration to determine whether tolerance to the drug would develop.

Pharmacology

Guanethidine (Su 5864) is [2-(octahydro-1-azocinyl) ethyl] guanidine sulfate. It is a white crystalline powder soluble in water at pH 6.[1] The animal experiments of Maxwell and others have shown that it exerts a protracted action on the sympathetic nervous system, apparently at the postganglionic nerve terminals. These experiments indicated that guanethidine blocks the sympathetic nervous system by inhibition of the release and/or the distribution of the transmitter substances from the

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nerve terminals. By chemical means, Cass Kuntzman and Brodie[6] demonstrated the progressive depletion of norepinephrine in the heart muscle after the administration of guanethidine. Richardson and Butterfield[7] confirmed this observation of Cass and associates, and in addition showed the depletion of catecholamines in the aorta. Burn and Rand[8] postulated that under normal circumstances there is a continuous release of norepinephrine from the store in the vascular wall and suggested that such a release is responsible for maintaining normal vascular tone. The absence of continuous release was thought to render the vascular smooth muscle hypersensitive to norepinephrine but insensitive to tyramine and ephedrine whose effect depends upon the presence of norepinephrine. On intravenous administration of guanethidine in dogs, Page and others found an initial short period of about an hour of increased activity of the sympathetic nervous system manifested by considerable increase in arterial pressure followed by a prolonged period of inhibition.[4,9] They also noted less response to norepinephrine during the initial period of hypertension than during the later period of inhibition; they interpreted this as meaning initial release of catecholamines and later depletion similar to that produced by reserpine. From these observations Page and others have speculated that the antihypertensive action of guanethidine is produced not only by inhibiting the release of and or distribution of the transmitter substance but also by the depletion of the store of norepinephrine.

Additional studies showed increased cardiac contractility and output during the initial hypertensive phase,[10] whereas decreased contractility and output occurred as well as venous pooling during the later hypotensive period.[9] The venous pooling due to decreased venomotor tone results in decreased venous return and consequently decreased cardiac output.[11,12]

Although the mode of action of this drug still remains obscure, the single mechanism of increased release of norepinephrine with consequent depletion from the blood vessels and heart muscle could explain both the initial hypertension and later hypotension.

The excretion of the drug has been studied by Dollery[3] and others in a group of acidotic and alkalotic rats after a 5-mg. subcutaneous dose of C^{14} labeled guanethidine. The urinary excretion in the first 4 hours was 0.64 mg. in the acidotic and 0.58 mg. in the alkalotic rats, which suggests that urinary excretion of it was free from the influence of pH.

The absorption of this drug from the alimentary tract of rats was studied by comparing the amount of the drug excreted in the urine and the amount remaining in the gut 4 hours after an orally administered dose. In 2 of the 4 rats studied there were 8.2 and 6.0 times, respectively, as much remaining in the gut as was excreted in the urine during the same period, which indicates a poor absorption of the drug from the alimentary tract.[3]

In man, Dollery and associates have studied the tissue distribution by both chemical and radioisotopic methods. They found the highest concentration in the kidney by both methods. Their studies, using a chemical method, demonstrated that the urinary excretion by patients in the first 24 hours was approximately 50 per cent after an intravenous dose and 20 per cent after an oral dose; after 72 hours the amounts rose to 72 and 36 per cent, respectively.[3] When the drug was given orally, the rate of excretion was low in the first 2 hours and then rose to a maximum between the second and fourth hours; appreciable amounts were excreted even after 72 hours. The slow rate of excretion is related to its prolonged and cumulative action. It is excreted both as unchanged guanethidine and as three closely related metabolites.

The fall in blood pressure is greater when the patient is upright. In clinical studies the side effects noted by various investigators are diarrhea, parotid tenderness, nasal obstruction, bradycardia, weakness, tiredness, mental depression, and failure of ejaculation.[1-4,13-15] Breathlessness has been observed as a side effect even after control of blood pressure.

Material and methods

Twenty-eight hypertensive patients who were followed in the Hypertension Clinic of Firmin Desloge Hospital form the basis of this study. There were 27 women and 1 man; their ages ranged from 32 to 72

years 9 were Caucasians and 19 were Negroes. All had essential hypertension the duration of which ranged from 6 months to 31 years and they had been followed in this clinic from 1 to 7 years. Associated conditions included obesity in 10 diabetes mellitus in 4 and angina pectoris, glaucoma epilepsy peptic ulcer anemia, osteoarthritis, and bilateral carcinoma of the breast in individual patients.

All patients had a history physical examination and a laboratory investigation which included complete blood count urinalysis, serum nonprotein nitrogen phenolsulfonphthalein excretion electrocardiogram chest x-ray film and intravenous pyelogram. A phentolamine test was done whenever the diastolic blood pressure was persistently elevated over 110 mm Hg Each patient was followed by the same doctor throughout the study

During each visit to the clinic four determinations of blood pressure were recorded the first was taken with the patient in the sitting position the second immediately afterward with the patient in the supine position the third 10 minutes later with the patient in the supine position and the fourth immediately after the patient had assumed the erect position The third and fourth recordings of blood pressure were used in compiling the results of this study The control blood pressure was determined by averaging the blood pressures taken weekly for a minimum of 4 weeks prior to treatment When evaluation was completed each case was presented to the Hypertension Conference before guanethidine therapy was started

The severity of the hypertensive disease was assessed by using Goodyer's severity index.[17] The severity index of the patients ranged from 2 to 24 however since in the majority the index was under 15 they were classified as having mild or moderate hypertensive disease.

The 28 patients included in this study were divided into three groups, as follows Group I was composed of 9 untreated patients whose only therapy was guanethidine Group II was composed of 12 patients who had previously been treated with trimethidinium and or ancillary medications the former were replaced by guanethidine and the ancillary medications were continued Group III was composed of 7 patients previously treated with trimethidinium thiazide compounds and or hydralazine all of which were replaced by guanethidine.

Grading of therapeutic response was done as follows an excellent response was considered to have been achieved when the diastolic pressure was consistently less than 95 mm. Hg while the patient was standing and the side effects were minimal or absent a moderate response was present when the *standing* diastolic pressure was consistently between 95 and 105 mm. Hg and side effects were no more than moderate a fair response was achieved when the standing diastolic pressure was above 105 mm Hg but showed a significant reduction (15 mm Hg or greater) or when the diastolic pressure was inconsistently reduced to levels below 105 mm. Hg and when side effects were no more than moderate a poor response was considered to have occurred when the standing diastolic pressure was inconsistently reduced to levels above 105 mm Hg or when side effects were severe

Side effects were graded from 1 plus to 3 plus 1 plus represented mild reactions which did not interfere with ordinary activity 2 plus represented moderate side effects which occasionally interfered with normal activities and 3 plus represented side effects which resulted in inability to perform normal activity Diarrhea as a side effect was classified as follows 1 plus represented two to three bowel movements a day and not requiring any medicinal therapy 2 plus represented three to five bowel movements a day and responding to medicinal therapy and 3 plus represented five or more bowel movements a day but not responding to medicinal therapy and necessitating the discontinuation of guanethidine therapy

A side effect index was derived by multiplying the numerical value of the severity of the side effect (1 2 or 3 plus) by the number of patients having this severity and then multiplying this product by the average number of days this side effect occurred each month. This was done for each of the three grades of severity and these three values were then added to-

*Kinal supplied by Wyeth Laboratories.

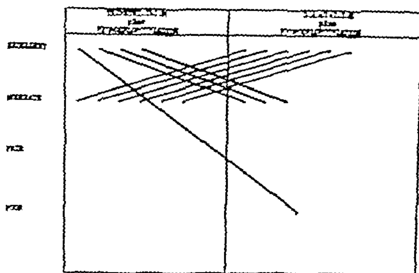


Fig. 1. Comparison of therapeutic responses in 14 patients.

gether this final value was designated as the side effect index. The side effect index ratio was obtained by dividing the value of the side effect index of the guanethidine study period by that derived from the last 3 months of the previous study period. This ratio gave a comparison which took into account all three factors required to judge side effects, namely severity, incidence, and duration.

Guanethidine was started in a dose of *12.5 mg. once daily before breakfast. It was* increased at weekly intervals by 12.5 mg. daily until normotension in the standing position was achieved or until limiting side effects developed, e.g., orthostatic hypotension.

Diet was unrestricted and was limited in sodium only if the patient was in congestive heart failure.

Patients in Group II were started on guanethidine which was gradually increased as mentioned above. Simultaneously trimethidinium was gradually reduced without changing any ancillary medications. Patients in Group III had all antihypertensive drugs gradually decreased as guanethidine was started and increased. This period of substitution of guanethidine for other antihypertensive agents is referred to as the transition period.

In the patients of Groups II and III the blood pressure response was compared to that observed during the last 3 months of the previous therapy. In all groups the response to guanethidine was determined by averaging the blood pressures from the fourth, fifth, and sixth months of therapy. In those patients receiving guanethidine for a longer period the response was also determined for the seventh to ninth months and tenth to twelfth months of therapy. This was done to determine whether there was any difference in the blood pressures during longer periods of therapy.

Results

The effects of guanethidine on the blood pressure, the severity indices, the side effects, and the therapeutic response are shown in Tables I-IV and Figs. 1 and 2.

The therapeutic response of the 9 patients of Group I after therapy with guanethidine was excellent in 8 (89 per cent). One patient had a poor response after 6 months, followed by a moderate response in the subsequent 3 months of therapy. During the control period 3 of the 9 patients (33 per cent) had severity indices which indicated mild hypertensive disease and 6 (67 per cent) moderate. At the end of therapy 4 (44 per cent) had mild and 5 (56 per cent) had moderate hypertensive disease.

No significant side effects were observed during guanethidine therapy. Two patients had diarrhea which was of 1 to 2 plus severity. The average daily dose of guanethidine was 63.7 mg. from the fourth to the sixth months of therapy.

Prior to therapy with guanethidine 6 (50 per cent) of the 12 patients of Group II had an excellent response to the previous medications, and 6 (50 per cent) had a moderate response. After therapy with guanethidine 8 (67 per cent) had an excellent response 3 (25 per cent) a moderate response and 1 (8 per cent) a poor response (Fig 1)

Before therapy with guanethidine 6 patients (50 per cent) had severity indices which indicated mild hypertensive disease 5 (42 per cent) moderate and 1 (8 per cent) severe. One patient in the moderate group originally had malignant hypertension (Fig 1) After treatment 9 (75 per cent) had mild and 3 (25 per cent) had moderate hypertension

As shown in Table III the side effects which showed the highest indices during the 3 months before the transition period were blurring of vision and dryness of mouth Other side effects during this period were weakness headache, constipation and symptomatic postural hypotension During the transition period there was a marked reduction in the side effect indices of blurring of vision dryness of mouth weakness, and constipation No significant change was observed in the side effect index of headache, whereas there was a slight increase in postural hypotension and a marked increase in dizziness. Three of the 12 patients in this group account for the increase in dizziness, and postural hypotension this increase occurred between the second and third weeks of the transition period corresponding with an increase in the dose of guanethidine From the fourth to the sixth months of therapy with guanethidine there was further decrease in the side effect indices of blurring of vision dryness of mouth and constipation Weakness increased minimally There was a marked reduction in the indices of postural hypotension and dizziness and no significant change in headache Six patients had diarrhea which was of 1 to 2-plus severity the frequency was slightly greater during the first month of therapy in 5

Prior to the transition period the average daily dose of trimethidinium in the 12 patients was 261 mg whereas the dose of guanethidine from the fourth to the sixth months of therapy was 73 mg Milligram for milligram the ratio of trimethidinium to guanethidine was 3 1 to 1 Of the group 10 (83 per cent) received hydrochlorothiazide in an average daily dose of 130 mg 4 (33 per cent) hydralazine 400 mg daily 2 (17 per cent) chlorothiazide 1,500 mg daily and 1 (8 per cent) rauwolfia 1 mg daily The average daily doses of the ancillary medications were not altered throughout the study

In Group III before the transition period 5 patients (71 per cent) had an excellent response to the previous medications and 2 (25 per cent) had a moderate response. After therapy with guanethidine 6 (86 per cent) had an excellent response and 1 (14 per cent) had a moderate response. Before therapy with guanethidine 5 patients (71 per cent) had severity indices which represented mild hypertensive disease and 2 (29 per cent) moderate After treatment with guanethidine 6 patients (86 per cent) had mild and 1 (14 per cent) moderate hypertensive disease.

Dizziness had the highest index during the 3 months before the transition period During the transition period there was an increase in the side effect indices of weakness, postural hypotension and headache, whereas there was a marked decrease in the index of dizziness. Between the fourth and the sixth months of guanethidine therapy the index of postural hypotensioe

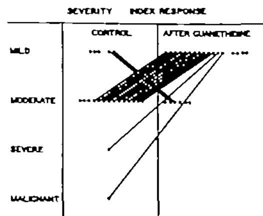


Fig 2 Each dot in the first column repres ts the control severity index of ach patient The data i the second colum how the severity index reponse after treatment with guanethidine Dot connected by l nes show variations in response Dot not connected by lines indicat no hange in response.

Table I Blood pressure response to guanethidine and previous therapy

Group	Control		Last 3 months of previous therapy		Transition		On guanethidine	
	Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing
I	192/115	176/113					175 (8.3%)† / 108 (6%)	133 (18%) / 87 (23%)
II	209/123	189/120	161 (23%) / 97 (21%)	147 (22%) / 92 (23%)	149 (21%) / 93 (24%)	135 (28%) / 85 (29%)	153 (24%) / 93 (24%)	141 (25%) / 90 (25%)
III	192/115	184/114	150 (23%) / 92 (20%)	137 (26%) / 92 (19%)	152 (20%) / 89 (22%)	135 (26%) / 87 (23%)	156 (18%) / 94 (18%)	136 (26%) / 90 (21%)
I II III Average blood pressure	197/117	183/116					161 (18%) / 98 (16%)	143 (22%) / 89 (23%)
II and III Average blood pressure	200/119	186/117	155 (23%) / 94 (21%)	142 (27%) / 92 (22%)	150 (25%) / 91 (23%)	135 (27%) / 86 (26%)	154 (23%) / 94 (21%)	138 (25%) / 90 (24%)

Averages from the fourth to the sixth months
†The percentage of blood pressure reduction was determined from the control values.

increased further but this was due to an increase of this side effect in only 1 patient of the whole group. There was a decrease in the index of weakness the other side effects remained essentially unaltered (Table III) Only 2 patients developed diarrhea of 1 to 2-plus severity One of these had it for 6 months and required paregoric three to four times a week the other had it during the first month of therapy but required no treatments.

Prior to the transition period 2 patients received trimethidinium in an average daily dose of 114 mg 6 hydrochlorothiazide 108 mg daily 3 hydralazine, 196 mg daily 1 rauwolfia 0.5 mg daily and 1 chlorothiazide 1 000 mg daily These medications were progressively decreased and totally discontinued at the end of the transition period simultaneously guanethidine was again increased after the end of the transition period and given in an average daily dose of 82 mg from the fourth to the sixth months of therapy

The effects of guanethidine therapy on the blood pressure of the three groups combined are shown in Tables I and II

The therapeutic response was excellent in 23 patients (82 per cent) and moderate in 5 (18 per cent) The average daily dose of guanethidine during the fourth to the sixth months of therapy was 73 mg Eight of the 9 patients had no further increase in medication and 1 had an increase of 12 5 mg from the seventh to the ninth months

During the control period 10 patients (36 per cent) had severity indices which indicated mild hypertensive disease 16 (57 per cent) moderate 1 (3.5 per cent) severe and 1 (3 5 per cent) malignant. After therapy with guanethidine the severity of the hypertensive disease was mild in 19 (68 per cent) of the patients and moderate in 9 (32 per cent) as shown in Fig 2 As shown in Table IV during guanethidine therapy postural hypotension headache and weakness had the highest indices. Ten patients (36 per cent) developed minimal or moderate diarrhea

The average pulse rate when the patients were supine during the control period was 81 beats per minute and on casual readings during guanethidine therapy it was 75 There was no significant change in the average weight of the patients.

During treatment 1 patient developed hemiparesis associated with marked hypotension and required hospitalization When

the daily dose of guanethidine was reduced from 25 mg to 12.5 mg there was a resumption of normal blood pressures, and the hemiparesis gradually disappeared This is the patient whose therapeutic response was considered to be poor the cerebral thrombosis was secondary to the marked hypotension.

Another patient, who became pregnant after the initiation of guanethidine had an uneventful delivery of a normal infant during the eighth month of pregnancy The blood pressure values were normal before and after delivery

One patient with malignant hypertension was not included in the study because the duration of guanethidine therapy was too short. In the 11 weeks he received guanethidine there was a reduction in the blood pressure values from 200/140 supine and 200/140 mm Hg standing to 160/95 supine and 150/85 mm. Hg standing This patient also received hydralazine 400 mg daily and hydrochlorothiazide, 150 mg daily While he was on this medication papilledema disappeared and the blood urea nitrogen became normal.

Discussion

Many clinical studies suggest that guanethidine should be reserved only for the more severe or the resistant cases of hypertension in which the blood pressure is not controlled by milder antihypertension drugs.[1,13,14,16,19] This assumption has not been validated by documented disadvantages of its use in mild or moderate hypertension It is apparently based upon the traditional concept that potent drugs with serious side effects such as the ganglionic blocking agents are indicated only in cases which are more severe or difficult to control Restriction to such cases appears to be unwarranted in regard to guanethidine since it does not produce the serious side effects of the ganglionic blocking agents To test this concept the present report is concerned mostly with patients whose hypertensive disease was mild or moderate. The duration of guanethidine treatment which lasted from 6 to 12 months, is comparable to the 9-month study of Dollery and associates.[3] Most studies have been of relatively short duration ranging from 8 days to 6 months, except for the recent 18-month study of Page and associates.[9]

The blood pressure response of the patients of Group I was excellent and only minimal side effects occurred These results are comparable to those of Frohlich and Freis[4] with a similar group of patients.

The 19 patients in Groups II and III whose blood pressure was previously controlled by trimethidinium and or ancillary medications maintained their normotension during the transition period and after substitution of guanethidine for the previous therapy These observations indicate that guanethidine is at least as potent as trimethidinium in lowering blood pressure

Table II Average blood pressure of patients on guanethidine therapy more than 6 months

	Control		Transition		4-6 months		7-9 months		10-12 months	
	Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing
Group I (4 patients)	192/118	187/117			187/114	147/94	172/107	134/87		
Group II (3 patients)	200/126	180/118	150/96	123/84	144/95	131/85	147/94	125/85		
(1 patient)	173/99	164/97	152/84	139/95	161/94	156/95	165/94	161/93	187/96	138/87
Group III (1 patient)	235/126	210/127	156/92	114/78	201/103	139/87	176/104	128/81		

*Table III Comparative side effect indices**

Side effect	Group I	Group II				Group III			
	During guanethidine	During 3 mo prior to treatment	Transition	During guanethidine	Index ratio	During last 3 mo prior to treatment	Transition	During guanethidine	Index ratio
Constipation	0	13 88	1 62	0	0	2 55	1	0	0
Dryness of mouth	0	85 98	8 14	1 66	01	1 1	0	0	0
Blurred ision	0 33	89 46	10 14	1 66	01	0	0	2 33	0
Weakness	3	28 74	4 32	8 66	30	3 66	14	4 56	1 02
Dizziness	0 66	5 22	26 33	1 66	31	10 35	0 14	1 00	009
Postural hypotension	0	13 28	21 32	4 0	0 30	3 33	9 5	23 33	7 06
Headache	3 32	19 62	18	20 64	1 0	99	6	6 66	6 72

*See description under Material and Method

and is effective either when used alone or in combination with other drugs.

The patients of Group I experienced no parasympathetic side effects, and the patients of Groups II and III no longer had significant symptoms of parasympathetic blockade after guanethidine was substituted for trimethidinium (Table III) Even though there was a significant reduction in the blood pressure of the patients of Group I when they were in the standing position no symptoms suggestive of postural hypotension were noted The severity indices of dizziness and postural hypotension of patients in Group II increased during the transition period but regressed during guanethidine therapy In Group III the slight increase in the severity index of postural hypotension during the transition period and during guanethidine therapy is the result of an increase of this side effect in just 1 of the 7 patients.

Others[7,23] have demonstrated that relatively large initial doses of guanethidine, 50 or 100 mg daily produced postural hypotension in nearly 50 per cent of their patients, a situation which required decreases or discontinuation of the drug In contrast, these same observers noted that when the initial daily dose ranged from 10 to 30 mg with subsequent increases the incidence of postural hypotension was minimal. The relatively low incidence of postural hypotension in the subjects of the present study is apparently the result of the small initial daily dose (12 5 mg) of guanethidine and the gradual increment (12.5 mg) of the subsequent doses.

Ten patients experienced diarrhea It occurred primarily during the first few weeks of therapy Although there were gradual increases in guanethidine dosage the incidence of diarrhea diminished In no instance was it severe enough to require discontinuation of guanethidine. This observation is in agreement with that of others.[7-9,21,19] Other side effects, such as drooping of the eyelids, parotid tenderness nasal congestion tremors, mental depression retention of fluid and lupus erythematosus phenomena were not observed in this series. The patients in this study were not evaluated for exercise hypotension

In a comparison of trimethidinium with guanethidine, milligram for milligram in the patients of Group II guanethidine was 3 1 times more potent than trimethidinium This relationship was highly variable among individual patients the range of the ratios was 0.8 1 to 22 1 Although guanethidine is slightly more expensive than trimethidinium milligram for milligram the greater potency of the former makes it more desirable from an economic standpoint.

The average guanethidine dose of 73 mg daily in this series is comparable to the observations of others.[12-23] The wide varia

Table IV. Average side effect indices for the whole group during the fourth to sixth months of guanethidine therapy*

		Patients	*Day/patient/month*	*Side effect index*
Constipation				
	0			
	1+			
	2+			
	3+			
	Total	0	0	0
Dryness of mouth				
	0			
	1+	1	1 66	1 66
	2+			
	3+			
	Total	1		1 66
Blurred vision				
	0			
	1+	3	1 44	4 32
	2+			
	3+			
	Total	3		4 32
Weakness				
	0			
	1+	[illegible]	1 775	14 20
	2+	1	1	2
	3+			
	Total	8		16 20
Dizziness				
	0			
	1+	4	0 83	3 1.
	2+			
	3+			
	Total	4		3 32
Postural hypotension				
	0			
	1+	2	13 6(	2 33
	2+			
	3+			
	Total	2		27 42
Headache				
	0			
	1+	5	4 26	21 30
	2+	3	3 11	9 33
	3+			
	Total	8		30 63
Diarrhea†				
	0			
	1+	9	3 50	3 9
	2+	[illegible]	0 85	13 6
	3+			
	Total	10		41 5

*See description under Material and Methods.

†The severity indices of diarrhea were computed for the entire 6-month period of guanethidine therapy due to its prevalence beginning but relative insignificance during the fourth, fifth, and sixth months.

tion of guanethidine dosage in this study 3 to 220 mg is typical of that previously reported which ranged from 5 to 750 mg.[3,9,11,23,25]

The 16 patients of Groups I and III who were treated only with guanethidine required approximately the same dosage as the 12 patients of Group II who were receiving ancillary medication. This suggests that there may be no advantage in using ancillary medications with guanethidine. Leishman and associates[15] also noted no beneficial effect of hydrochlorothiazide when added to guanethidine. Since others[23,25] have stated that thiazide compounds potentiate the action of guanethidine, these controversial views warrant further investigation.

During the 6 to 12 months duration of this study no tolerance to the drug was noted. This is in accord with the observations of others.[3,4,9] However Leishman[15] has reported that a "few" of his 25 patients appeared to develop tolerance to guanethidine. The results of this study indicate that guanethidine may be safely used in cases of mild and moderate hypertension. The adequate reduction of blood pressure with relatively minimal side effects, as observed in the present report, supports this concept. The cerebral thrombosis which occurred in one patient as a result of marked hypotension probably could have been avoided by earlier reduction in the drug dosage.

Summary

A 6 to 12-month study of the effect of guanethidine has been carried out in a group of 28 patients with essential hypertension of varying degrees of severity.

The blood pressure response to an average daily dose of 73 mg. of guanethidine was 161/98 mm. Hg supine and 143/89 mm. Hg standing from control levels of 197/117 mm. Hg supine and 183/116 mm. Hg standing. These results are the average blood pressures during the fourth to sixth months of therapy.

The side effects were minimal when compared to those noted with trimethidinium, they were markedly decreased or absent.

Guanethidine is a very useful and versatile antihypertensive drug. It may be used singly or in combination with other drugs in cases of mild and moderate hypertension although less potent preparations may be preferable. In cases of more severe and malignant hypertension it may be employed in the initiation of therapy or it may be readily substituted for ganglionic blocking agents without loss of blood pressure control.

REFERENCES

1. Maxwell, R. A., Plummer, A. J., Schneider, F., Povalski, H., and Daniel, A. I.: Pharmacology of [2-(octahydro-1-azocinyl)-ethyl]-guanidine sulfate (Su 5864), J. Pharmacol. & Exper. Therap. 128:22, 1960.
2. Dollery, C. T., Emslie-Smith, D., and Milne, M. D.: Guanethidine in the treatment of hypertension, Lancet 2:381, 1960.
3. Frohlich, E. D., and Freis, E. D.: Clinical trial of Su 5864, Med. Ann. District of Columbia 28:419, 1959.
4. Page, I. H., and Dustan, H.: A new potent antihypertensive drug, J.A.M.A. 170:1265, 1959.
5. Richardson, D. W., and Wyso, E. M.: Effective reduction in blood pressure without ganglionic blockage, Virginia M. Month. 86:377, 1959.
6. Cass, R., Kuntzman, R., and Brodie, B. B.: Norepinephrine depletion as possible mechanism of action of guanethidine (Su 5864) a new hypotensive agent, Proc. Soc. Exper. Biol. & Med. 103:871, 1960.
7. Richardson, J. A., and Butterfield, J. L.: The effect of guanethidine on myocardial contractility and catecholamines, Symposium on Guanethidine, University of Tennessee College of Medicine, Memphis, April 22, 1960.
8. Burn, J. H., and Rand, M. J.: Action of sympathomimetic amines in animals treated with reserpine, J. Physiol. 144:314, 1958.
9. Page, I. H., Hurley, R. E., and Dustan, H. P.: Treatment of hypertension with guanethidine, J.A.M.A. 175:543, 1961.
10. Gaffney, T. E.: Effect of guanethidine and bretylium on the dog heart-lung preparation, Circulation Res. 9:83, 1961.
11. Imhof, P. R., Lewis, R. C., Page, I. H., and Dustan, H. P.: Effects of guanethidine on arterial pressure and vasomotor reflexes, Symposium on Guanethidine, University of Tennessee College of Medicine, Memphis, April 22, 1960.
12. Richardson, D. W., and Magee, J. H.: Influence of guanethidine on cardiac output and renal function, Symposium on Guanethidine, University of Tennessee College of Medicine, Memphis, April 22, 1960.
13. Baiermo, P. E.: Nova droga anti-hypertensiva Ismelina (Su 5864), Coimbra Med. (Port.) No. 4, 1960.
14. Evanson, J. M., and Sears, H. T. N.: Comparison of bretylium tosylate with guanethidine in the treatment of severe hypertension, Lancet 2:387, 1960.
15. Leishman, A. W., Mathews, H. L., and Smith,

A. S. Hypotensive drug with prolonged action, Lancet 2 1044 1959
16. Pigeon, C., Davignon, J. Beron, P., Trudel, J., Dufault, C., and Genest, J. Guanethidine administration in 28 hypertensive patients, Canad. M. A. J. 83:690 1960
17. Goodyer A. V. H., Rosenthal, E., and Jaegan, C. A. Clinical evaluation and management of hypertension, Yale J. Biol. & Med. 27:451 1955
18. Arnold, O. H., and Kaiser K. Die Behandlung schwerer Formen von Arteriellen, Hypertonie mit Guanethidin, Deutsche med. Wchnschr 85:28a, 1236 1960.
19. Bartorelli, C., Gargano, N., Regoli, D., and Zanchetti, A. Die Wirkung langdauerndes Guanethidin-Verabreichung auf die Nierenfunktion von Hochdruckkranken. Deutsche med. Wchnschr 85:28a, 1271 1960.
20. Eagan, J. T., and Orgain, E. S. A study of 38 patients and their response to guanethidine J.A.M.A. 175:550 1961.
21. Brest, A. N., and Moyer J. H. Newer approaches to antihypertensive therapy J. A. M. A. 172 1041 1960.
22. Cottier P., Reubi, F., and Dupasquier E. Die Wirkung von Guanethidin auf den Hochdruck und die Nierenfunktion bei klinischer und ambulanter Behandlung, Deutsche med. Wchnschr 85:28a, 1263 1960.

Electrocardiographic findings in concentric and eccentric left ventricular hypertrophy

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Electrocardiographic criteria for the recognition of left ventricular hypertrophy have been derived empirically from electrocardiographic-clinical and electrocardiographic-pathologic correlations. Electrophysiologic bases for the various electrocardiographic abnormalities seen in patients with left ventricular hypertrophy are uncertain, as has been pointed out in the recent comprehensive review of the subject.[1] The present study was prompted by the realization that little attention has hitherto been paid to whether the increase in left ventricular muscle mass was associated with a normal residual volume or combined with an increase in residual volume—that is, dilatation—in the left ventricular chamber. Thus, the purpose of this study is to compare the electrocardiographic features of cases of pure left ventricular hypertrophy in which, on clinical and pathologic grounds, the volume of the left ventricular cavity was thought to be normal with those of cases in which an appreciable dilatation of that chamber appeared to have been present.

Material and methods

The basis for this study was a comparison of a carefully selected group of cases in which there was eccentric and concentric left ventricular hypertrophy. The selection of cases was made as follows: (1) The only cases considered were those for which there were necropsy studies and a 12 lead electrocardiogram which had been taken during the terminal admission of the patient, not more than 2 months prior to death. (2) Lesser degrees of cardiac hypertrophy were eliminated and an arbitrary lower limit of 500 grams of cardiac weight was set. (3) Cases in which right ventricular hypertrophy was present were eliminated. For that purpose, only hearts with a ratio of average left ventricular to right ventricular wall thickness greater than three to one, and right ventricular wall thickness of 5 mm. or less were included in the series. (4) Cases in which there was clinical or pathologic evidence of coronary artery disease, myocardial infarction, or myocardial fibrosis were eliminated. (5) The smaller group thus derived was carefully reviewed from the standpoint of the size of the left ventricular chamber. Two criteria were used: the prosector's description of the left ventricle in regard to the presence or absence of dilatation, and the size of the cardiac shadow in the posteroanterior roentgenogram. Only cases were accepted

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in which these two criteria were fulfilled concurrently. Thus cases in which the heart was normal or nearly normal in size on the roentgenogram and cardiac dilatation was absent were considered to represent concentric left ventricular hypertrophy. Those hearts in which cardiomegaly was observed on the roentgenogram and dilatation was found at necropsy were considered to represent eccentric left ventricular hypertrophy. Cases in which there were equivocal findings by either of the two methods or in which there was a conflict between the two methods were excluded from the study. Thus, the final group of 30 cases of pure left ventricular hypertrophy which fell distinctly into the concentric or eccentric group was obtained. There were 16 cases of eccentric left ventricular hypertrophy and 14 cases of concentric left ventricular hypertrophy. From the former group 3 more cases were eliminated—those in which the heart weighed over 900 grams. This elimination was thought to be advisable because in the concentric group no cases of comparable heart weight were found.

Descriptions of the technical criteria for the acceptance of electrocardiograms and of autopsy techniques have been presented in earlier communications.[2,4]

Results

Tables I and II present detailed findings in the 27 cases that constitute the final series. Table I presents the data for the concentric hypertrophy series, Table II for the eccentric hypertrophy series. Both are arranged according to heart weight in decreasing order and, as can be noted, the corresponding case numbers in the two tables apply to cases with roughly comparable heart weights. The tables include the principal clinical diagnosis and the anatomic diagnoses with notes on the terminal event. Other pathologic data include measurements of the representative average thickness of the left ventricular and right ventricular walls and the prosector's opinion on the presence or absence of cardiac dilatation. Clinical data include the radiographic diagnosis of cardiomegaly, a notation of the presence or absence of cardiac failure at the time of the final hospital entry, and the question of whether digitalis was administered to the patient at the time his representative electrocardiogram was obtained. Electrocardiographic data are given in the remainder of the tables. The first column of electrocardiographic data represents the electrocardiographic diagnosis, that is, the result of a specific review of the electrocardiographic findings by one of the authors who had applied strict criteria as to the presence or absence of left ventricular hypertrophy. The voltage criteria tabulated are those of Sokolow and Lyon. The mean QRS axis was calculated on the basis of the total QRS complexes unless specified otherwise. Two criteria were applied in regard to the duration of ventricular activation, namely, the total QRS duration and the ventricular activation time measured in the customary manner. Depressions of the S-T segment were graded as being absent, questionable, mild, or severe. T wave abnormalities were presented as being absent, questionable (which implied flattening of the T waves), mild (which implied shallow inversion, diphasic or isoelectric T waves), or pronounced (which implied inverted T waves in the leads with maximum positive QRS complexes). The final column represents a transitional zone in the precordial electrocardiogram, namely, lead or leads in which negative QRS complexes changed into positive.

As can be seen from the table, left ventricular hypertrophy could be identified in 11 out of 14 cases in the concentric left ventricular hypertrophy series. In 1 case the findings were characteristic in that all the criteria were fulfilled. In others, left ventricular hypertrophy was identifiable by partial electrocardiographic criteria. The remaining 3 cases included 2 in which the tracing was considered to be within normal limits. In one patient, right bundle branch block was present and the initial QRS forces were entirely within normal limits.

The electrocardiographic diagnosis in the series of eccentric left ventricular hypertrophy permitted unequivocal diagnosis in 8 out of 13 cases. In 1, left ventricular hypertrophy was considered probable. In the other 4 cases, conduction defects were present, namely, right bundle branch block in 3 and left bundle branch block in 1. In 3

Table I Group I Concentric hypertrophy of the left ventricle summary of findings in 14 patients

Case number	Initials	Age (yr)	Sex	Clinical diagnosis	Anatomic diagnosis cause of death	Heart weight (Gm)	Heart wall thickness		Dilation of LV (anatomic)	Enlarged heart (radiologic)
							LV	RV		
1	B.T	40	M	Malignant hypertension	Nephrosclerosis pneumonia	840	22	4	±	±
2.	E.P	43	F	Hypertensive cardiovascular disease	Same cardiac failure	810	17	3	0	±
3.	N W	52	M	Rheumatic heart disease aortic stenosis	Same operative death	800	21	5	0	0
4	J J	49	M	Hypertensive cardiovascular disease	Same uremia	710	20	3	±	±
5.	D I	54	M	Hypertensive cardiovascular disease	Same uremia	700	17	4	0	0
6.	S.B	41	M	Hypertensive cardiovascular disease	Same uremia	680	25	3	±	±
7	N W	67	F	Hypertensive cardiovascular disease	Same	650	17	3	0	±
8.	B S	41	M	Hypertensive cardiovascular disease	Arteriolar nephrosclerosis uremia	600	18	3	0	±
9	M L.	33	M	Calcific aortic stenosis	Same bacterial endocarditis	580	18	3	0	±
10.	C H	45	M	Hypertensive cardiovascular disease	Same pneumonia	575	17	3	0	±
11	C.K.	58	M	Calcific aortic stenosis	Same carcinoma	560	17	4	0	0
12.	N G	37	M	Malignant hypertension	Arteriolar nephrosclerosis uremia	550	25	5	0	0
13.	R.S.	49	M	Hypertensive cardiovascular disease	Same, subarachnoid hemorrhage	525	17	3	0	0
14.	N I	36	M	Hypertensive cardiovascular disease	Same uremia	510	20	4	±	±

patients with right bundle branch block initial QRS complexes were considered to be within normal limits.

Voltage criteria were fulfilled in the majority of cases in both groups there was a wide variation of voltage from slightly increased above the norm to very high voltage of 9 6 millivolts. It is noted that the voltage criteria do not show a definite relationship to the heart weight nor does there seem to be any difference between the occurrence and severity of voltage increase between the two groups. A review of the mean QRS axis in both groups revealed that in most cases it was placed in the normal quadrant of from 0 to +90 degrees. A superior axis shift occurred in 4 cases of the concentric group and in 3 cases of the eccentric hypertrophy group. Only 3 patients in the entire series showed a left axis deviation of −30 degrees or beyond No difference in axis shift in the two groups appeared to be present. QRS duration was greater than 0 08 second in 5 patients of the concentric group and in 4 patients of the eccentric group excluding conduction defects. Ventricular activation time was prolonged beyond 0.05 second in 4 cases of the concentric group and in 3 cases of the eccentric group Depression of the S-T segment was present in the majority of cases in both groups. The S-T segments were isoelectric in 5 cases of each group. T waves were normal in only 1 case of eccentric left ventricular hypertrophy and in 3 cases of concentric left ventricular hypertrophy On the other hand minor T wave alterations were present in 3 cases of the concentric group and in 1 case of the eccentric group A transitional zone was shifted to the left

Heart failure (clinical)	Digitalis	Electrocardiographic diagnosis	*Electrocardiographic criteria*						
			QRS voltage RV + SV (mm)	Mean QRS axis	QRS duration (sec)	Ventricular activation time (sec)	S-T segment depression	T-wave inversion	Transitional zone
+	+	LVH+++	56	−10°	0.08	0.04	+	++	V
+	+	LVH+	50	−20°	0.08	0.03	±	±	V
±	+	LVH++	43	+75°	0.08	0.05	+	++	V
0	0	LVH++	72	+60°	0.10	0.06	+	++	V
±	+	LVH+	41	+30°	0.11	0.06	++	+	V
0	0	LVH+	78	+15°	0.10	0.06	0	+	V-V
+	+	LVH±	32	−30°	0.10	0.04	+	±	V
+	+	LVH++	70	0°	0.08	0.04	+	++	V
+	+	LVH++	53	−5°	0.08	0.04	++	+	V
0	0	Within normal limits	22	+30°	0.08	0.04	0	0	V
0	0	RBBB normal initial QRS	20	0° Init.	0.10	0.04	0	0	V
0	0	LVH++	96	0°	0.10	0.06	++	++	V
0	0	LVH+	70	+45°	0.08	0.04	0	±	V
0	0	Within normal limits	28	+30°	0.08	0.04	0	0	V

in most cases of both groups, with Lead V₃ considered to be the limit of normal. There were no trends which showed a difference in the transitional zone between the concentric and eccentric hypertrophy groups. The influence of the administration of digitalis on the depression of S-T segments and inversion of the T waves appears to have been rather small. It is noteworthy that digitalis was not given to the 2 patients whose tracings were considered to be within normal limits. Otherwise it is apparent that S-T depression and T wave inversion of appreciable degree occur frequently without administration of digitalis.

Discussion

Electrocardiographic criteria for left ventricular hypertrophy fall into three categories, two of which pertain to the process of depolarization of the ventricles and the third to the process of their repolarization. Both the origin and the significance of the alterations in the electrocardiogram found in patients with left ventricular hypertrophy are still a matter of considerable controversy and the theoretical basis for the electrocardiographic pattern of left ventricular hypertrophy is not clear.[1] The process of depolarization of the ventricles found in patients with left ventricular hypertrophy is a mere exaggeration of the normal in that the magnitude and the duration of the QRS forces are frequently increased. The difficulty in separating the normal from the abnormal and the inaccuracy in electrocardiographic diagnosis are in the most part related to the fact that clinical electrocardiography uses indirect distant leads wherein electrical forces can-

not be presented in a quantitative way since they are affected by such extraneous factors as proximity of the heart to the chest wall, conductivity of intermediate tissues, body build, and so on. Changes which affect the process of repolarization are qualitative rather than quantitative and therefore would appear to be more reliable. However, their significance is even less clear, for such changes can be caused by many factors other than left ventricular hypertrophy. Furthermore, their development in left ventricular hypertrophy is considered by some to be an integral part of the increased muscle mass, by others to be due to the hemodynamic factor of the increased intramural tension, and by still others to be a consequence of the purely secondary factor of complicating ischemia. The rather vague term of "strain" is frequently used which implies that the abnormality of the repolarization signifies another additional process over and above the hypertrophy of the left ventricle.

This study of a comparison of the findings in concentric and eccentric hypertrophy was undertaken for two reasons. In the first place, it was thought that if the two different pathophysiologic forms of left ventricular hypertrophy differ electrocardiographically, it might be possible to shed some light on the genesis of electro-

Table II. Group II. Eccentric hypertrophy of the left ventricle: summary of findings in 13

Case number	Initial	Age (yr.)	Sex	Clinical diagnosis	Anatomic diagnosis; cause of death	Heart weight (Gm.)	Heart wall thickness LV	Heart wall thickness RV	Dilation of LV (anatomic)	Enlarged heart (radiologic)
1	C.W.	45	M	Calcific aortic stenosis	Same; operative death	875	20	3	+++	++
2.	R.B.	52	M	Rheumatic heart disease, aortic stenosis	Same; cardiac failure	850	21	5	+++	++
3	C.B.	36	M	Rheumatic heart disease, aortic insufficiency	Same; cardiac failure	800	20	3	++	+++
4	W.P.	63	M	Rheumatic heart disease, aortic stenosis	Same; pulmonary infarcts	720	16	3	+++	++
5	R.W.	38	M	Chronic glomerulonephritis	Same; uremia	700	16	4	++	+++
6	J.M.	65	M	Syphilitic heart disease, aortic insufficiency	Same; cardiac failure	660	20	4	++	++
7	J.R.	31	M	Rheumatic heart disease, aortic insufficiency	Same; operative death	650	20	4	++	+++
8.	R.A.	48	M	Calcific aortic stenosis	Same; cardiac failure	610	17	3	+	++
9	L.D.	28	M	Chronic glomerulonephritis	Same; uremia	600	15	3	++	++
10.	L.M.	42	M	Rheumatic heart disease, aortic insufficiency	Same; cardiac failure	575	16	3	++	++
11	G.M.	41	M	Hypertensive cardiovascular disease	Same; cardiac failure	550	17	4	++	++
12	A.F.	52	M	Rheumatic heart disease, aortic stenosis and insufficiency	Same	520	15	3	++	++
13	C.L.	24	M	Rheumatic heart disease, aortic stenosis and insufficiency	Same	500	20	4	++	++

cardiographic changes seen in left ventricular hypertrophy. In the second place the study was a means of investigating and testing the validity of a hemodynamic approach to ventricular hypertrophy which was first suggested by a Mexican group of investigators. In 1952 Cabrera and Monroy[4,6] brought forth the concept of systolic and diastolic overload of the right and left ventricles. These authors recalled that the original Starling experiments with heart-lung preparation demonstrated two ways by which cardiac work can be increased to the point of failure: (a) overload due to increased output; (b) overload due to increased resistance. Inasmuch as hypertrophy of the heart is a physiologic response to increased work, it follows that either increased cardiac output or increased peripheral resistance will lead to cardiac hypertrophy. The work of the heart against *increased resistance or systolic overload* occurs in the systemic circulation in response to arterial hypertension or aortic stenosis. Its physiologic substrate is left ventricular systolic hypertension and pathologically they represent examples of concentric hypertrophy in which the cavity of the left ventricle is not increased by large residual volume except in the late stages when the left ventricle becomes grossly incompetent. Increased work of the left

patients

Heart failure (clinical)	Digitalis	Electrocardiographic diagnosis	*Electrocardiographic criteria* QRS voltage RV + SV (mm.)	Mean QRS axis	QRS duration (sec.)	Ventricular activation time (sec.)	S-T segment depression	T-wave inversion	Transitional zone
+	+	LVH+++	90	0°	0.10	0.05	++	++	V
+	+	LVH+++	80	+15°	0.08	0.05	++	++	V–V
+	+	LVH++	45	−10°	0.08	0.06	++	+	V
+	0	RBBB normal initial QRS	24	−45° Initial	0.12	0.05	0	+	—
+	+	LVH±	44	+45°	0.08	0.05	0	±	V
+	+	RBBB	28	+75° Initial −105 Terminal	0.10	0.06	+	0	V
+	+	LVH+++	58	+30°	0.09	0.05	++	++	V
+	+	LBBB	90	−30°	0.14	0.10	++	++	V
+	+	LVH+	40	+90°	0.06	0.03	+	+	—
+	+	RBBB normal initial QRS	25	+110°	0.12	0.05	0	+	—
+	+	LVH+	28	+30°	0.09	0.05	+	++	V
+	+	LVH+	29	+45°	0.10	0.06	0	++	V
+	+	LVH+	37	+45°	0.07	0.04	0	+	V

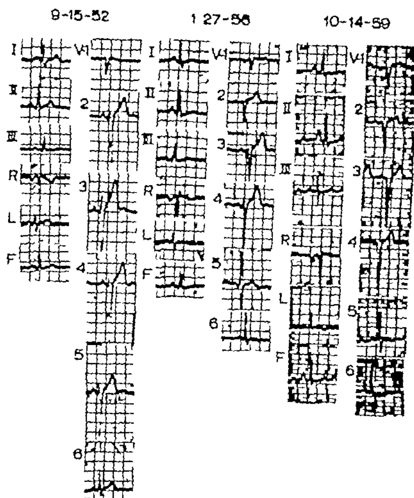


Fig. 1. Serial electrocardiographic changes in a patient with concentric hypertrophy of the left ventricle showing gradual development of S-T T abnormalities. (Half standardization in precordial leads in middle and right record.)

ventricle due to abnormally large stroke volume occurs in patent ductus arteriosus and in aortic insufficiency. In these conditions residual volume is large and dilatation ensues early, leading to eccentric left ventricular hypertrophy. Thus from the pathophysiologic standpoint concentric left ventricular hypertrophy represents conditions of left ventricular systolic overload before the onset of gross and probably long-standing cardiac failure. Eccentric hypertrophy represents instances of diastolic overloading of the left ventricle and end results of systolic overload. Electrocardiographic features of the two types of overload according to these authors[3] are as follows: diastolic overload of the left ventricle produces an increase in the size of the R and T waves in leads which reflect primarily left ventricular potential; systolic overload of the left side causes flattening or inversion of T waves and depression of the S-T segments in these leads. This hemodynamic approach to the electrocardiographic patterns of ventricular hypertrophy has in the last few years enjoyed great popularity, particularly in connection with congenital heart disease. It is of interest to note that one of the original authors felt recently the need to restate and clarify his position,[4] explaining that the hemodynamic approach to electrocardiography suggested by him represents trends rather than precise diagnostic criteria. It is also noteworthy that neither the original authors nor other investigators

who accepted the concept subjected it to a critical evaluation by electrocardiographic hemodynamic correlation in a sizable group of cases or by electrocardiographic pathologic correlation but rather satisfied themselves with a presentation of electrocardiograms in key cases which exemplified various hemodynamic conditions.

In an interpretation of the results of this study it should be pointed out that the rigid criteria for selection left only a small series of cases. However by the very process of selection it was possible to produce a fairly evenly matched group of cases in which the only variable was that in one section the left ventricular cavity appeared to be normal and in the other section dilatation was present in addition to the hypertrophy No trend could be found to suggest that the two groups could be electrocardiographically identified in any way With only the exception of the more common occurrence of conduction defects in the eccentric hypertrophy group all the electrocardiographic criteria were represented to a comparable extent in the two groups. In this small group of cases the difference in the incidence of conduction defects does not appear to be significant Thus it appears highly probable that the presence or absence of cardiac dilatation is immaterial to the development of the pattern of left ventricular hypertrophy in the electrocardiogram. Results of this study reaffirm a relationship between the increase in muscle mass of the left ventricle and the electrocardiographic deviations from the norm that represent the pattern of left ventricular hypertrophy Furthermore they tend to cast serious doubt upon the various theories of the origin of this pattern that bring into the picture dilatation of the left ventricular chamber and its possible effect upon the conduction system upon the position of the left ventricle in relation to the chest wall and upon the intracardiac blood volume.[1] Finally our results provide a significant argument against the alleged electrocardiographic recognition of systolic and diastolic overload of the left ventricle, because of the electrocardiographic similarities between cases with concentric and those with eccentric left ventricular hypertrophy the former exemplifying systolic and the latter diastolic overload. Specifically Cabrera and Monroy[4] postulated early inversion of T waves in systolic over loading of the left ventricle (concentric hypertrophy) and a persistence or exaggeration of upright T waves in diastolic overloading of the left ventricle (eccentric hypertrophy) This has not been the case in this series in fact the opposite may be surmised by the fact that normal repolarization has been found more often in concentric than in eccentric left ventricular hypertrophy

As a by product of this study a few findings deserve comment. The poor correlation between the delay in ventricular activation and the total QRS duration and the presence of left ventricular hypertrophy which has been commented on earlier[8] finds further confirmation in this study It can also be implied that the depression of the S-T segment and inversion of the T wave is a direct effect of left ventricular hypertrophy rather than a complication due to strain or coronary insufficiency The gradual development of left ventricular hypertrophy of the concentric type is exemplified in Fig 1 wherein the patient s serial electrocardiograms show different stages of its formation The administration of digitalis appears to speed up S-T-segment depression and T wave inversion but these changes develop also without the administration of this drug as an integral part of the pattern of left ventricular hypertrophy It should also be pointed out that the observation of Abdin [7] who suggested that T wave alterations in aortic stenosis are more pronounced than in hypertension implying an element of coronary insufficiency in the former is not confirmed in this study

Summary and conclusions

This study was designed to compare electrocardiographic findings in patients with necropsy proved concentric left ventricular hypertrophy in which the cavity of the left ventricle was normal with those in patients with eccentric left ventricular hypertrophy wherein an appreciable degree of cardiac dilatation accompanied left ventricular hypertrophy Only definitely hypertrophied hearts were included in the series the lower limit of heart weight was 500 grams. All cases in which there was con

comitant right ventricular hypertrophy and coronary artery disease or myocardial changes were eliminated and from the remainder only cases with clear-cut concentric or eccentric hypertrophy were obtained eliminating inconclusive intermediate cases The final group for comparison consisted of 13 cases of eccentric left ventricular hypertrophy and 14 cases of concentric left ventricular hypertrophy in which cardiac weights were comparable A careful analysis of the electrocardiographic findings revealed no difference in the occurrence of the various electrocardiographic criteria with the sole exception of the somewhat more common occurrence of conduction defects in the group of patients with eccentric left ventricular hypertrophy On the basis of this study the conclusion was reached that the presence or absence of dilatation does not appear to influence the electrocardiographic pattern of left ventricular hypertrophy and that that pattern presumably depends on the increase in muscle mass The findings are dis-
...d in the light of the electrophysiologic ...ens of the pattern of left ventricular hypertrophy particularly in view of their relationship to the hemodynamic type of overloading of the left ventricle The findings are considered to be significant points against the view that in left ventricular hypertrophy the electrocardiographic abnormalities due to systolic overload are different from those due to diastolic overload

REFERENCES

1 Scott R. C The correlation between the electrocardiographic pattern of ventricular hypertrophy and the anatomic findings Circulation 21:256, 1960
2 Selzer A., Ebnother C L., Packard P Stone V O and Quinn J E. Reliability of electrocardiographic diagnosis of left ventricular hypertrophy Circulation 17:255 1958.
3 Selzer A York E., Naruse D Y and Pierce, C H Electrocardiographic findings in 500 cases with hypertrophy of cardiac ventricles, Am. J M Sc 240:543 1960
4. Cabrera E and Monroy J A Systolic and diastolic loading of the heart. I Physiological and clinical data, Am. Heart J 43:661 1952
5 Cabrera, E., and Monroy J A Systolic and diastolic loading of the heart. II Electrocardiographic data, Am Heart J 43:669 and 686, 1952.
6. Cabrera, E. and Gaxiola, A. A critical re-evaluation of systolic and diastolic overloading patterns, Prog Cardiovas Dis. 2:219 1959
7 Abdin, Z H. The electrocardiogram in aortic stenosis, Brit. Heart J 20:31 1958.

Triparanol (MER-29) therapy in office practice

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Triparanol is now widely used in the control of hypercholesterolemia and hopefully, as a possible means of slowing atherogenesis, particularly in ischemic heart disease. Our early experience[1] accorded with observations of others: serum cholesterol content decreased in most of 10 office and hospital outpatients and complaints of angina pectoris diminished in some of these. Aspects of this use of the drug and of its mode of action have been reviewed editorially[2] and in correspondence by one of us.[3] The specific effect of the drug is to impair saturation of the $C_{24,25}$ bond of desmosterol—which may be the immediate intermediary precursor of cholesterol—so that the net effect is that serum of treated patients contains a mixture of cholesterol and desmosterol, and total serum sterol and cholesterol synthesis is usually, but not always, diminished.

The present report is based on experience in office patients seen by one of us (H.A.Z.). It describes observations of serum cholesterol, clinical status in ischemic heart disease, and the side effect of loss of hair.[4]

Patients were grouped as having ischemic heart disease (IHD) if they had sustained a myocardial infarct (MI) or showed symptoms or electrocardiographic signs of coronary insufficiency (CI) in some with preceding MI (MI+CI). Electrocardiograms (12-lead, 3 standard, 3 unipolar limb and 6 precordial leads) were recorded before and at the end of the period of observation; diagnoses of CI were usually made from records obtained in standard or double Master step tests. Determinations of serum total lipids, phospholipids, and total cholesterol (the latter by the method of Abell and associates[4]) were made at the beginning and end of the periods of treatment. Triparanol was given in doses of 250 mg. daily and this was increased to 500 mg. daily in several patients whose serum cholesterols were not diminished by the lower dose. Most patients had previously been on fat restricted diets, and those with CI took twice-daily doses of long-acting pentaerythritol tetranitrate; these regimens were maintained unchanged during treatment with triparanol. Periods of treatment averaged 11 months and ranged from 1 to 18 months: 4 patients were observed only for 1 to 4 months, 18 for 4 to 8 months, 20 for 8 to 12 months, 21 for 12 to 16 months, and 8 for 16 to 18 months; thus the mean period represents the median. Data listed below are from observations during triparanol therapy. The few patients who reacted with rashes or gastric intolerance are not listed since in these the treatment was promptly discontinued.

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Table I. Distribution of patients by age, sex, and diagnosis

Diagnosis: Group	Diagnosis: Subgroup	Age classes: 30-39 M	30-39 W	40-49 M	40-49 W	50-59 M	50-59 W	60-69 M	60-69 W	70-71 M	70-71 W	Totals
IHD												58
	MI	2		2		5		9	1	2		21
	CI			6		2	7	8	2			25
	MI + CI	1		2		4	1	3	1			12
HC												
	Hypertension			1		1	1		1			4
	Arteriosclerosis					1	2		1			4
	Other	1		2		1	1					5
Totals		4		13		14	12	20	6	2		71

Distributions as indicated in the text. *IHD*, ischemic heart disease; *MI*, remote myocardial infarct; *CI*, coronary insufficiency; *HC*, hypercholesterolemia.

Results

Distribution of patients by age, sex, and diagnosis is shown in Table I. Primary diagnosis in 58 of the 71 patients was IHD; 21 of the 58 were women; the largest proportion, 31, were men under 60 years of age. The other 13 patients were placed on triparanol because of hypercholesterolemia (HC) associated with hypertensive vascular disease, generalized arteriosclerosis, or without apparent disease.

Table II summarizes responses to triparanol therapy. Triparanol diminished "apparent"* serum cholesterol content by about 12 per cent in the group as a whole and equally in the IHD and HC groups. The numbers of patients in age, sex, and diagnostic subgroups are too small to suggest a significant difference between subgroups. Mean pretreatment serum cholesterol content of men with MI is higher in those under 60 years of age than in those 60 to 71 years of age; this accords with the experiences of others, but the difference in these small series is not statistically significant. Table III assembles data from all subgroups arranged in order of increasing cholesterol content. Ratios of final to initial serum cholesterol content indicate that triparanol decreased cholesterol by some 19 per cent *only* in patients with initial levels averaging 260 mg. per 100 ml. or more, and that the response was not increased with further increments in initial level. Statistical calculation indicates that the difference in response between those with less and those with more than 260 mg. per 100 ml. is highly significant.

Table IV summarizes clinical observations that seemed favorable. Subjective improvement was listed if the patient volunteered that angina had subsided. Electrocardiographic improvement was listed if signs of postexercise myocardial ischemia (based on considerations similar to those of Dimond[7]) diminished to normal responses during treatment. On these bases, 5 of 25 anginal patients improved subjectively and 3, including 1 with subjective improvement, improved electrocardiographically. These changes were noted at from 5 to 15 months after treatment was begun. In contrast, 2 patients—both initially hypercholesterolemic (serum cholesterol more than 300 mg. per 100 ml. and responses to treatment of about −20 per cent)—developed signs of increased coronary insufficiency while under treatment.

The only side effect observed was loss of

*The term "apparent" is used for analyses during treatment because desmosterol contributes to the blue-green color of the reaction, so that what is measured as cholesterol is "apparent serum cholesterol," i.e., cholesterol plus a fraction of circulating desmosterol.

hair Experience is summarized in Table V In one case (Patient No. 5) the change was severe, with loss of body hair and cutaneous changes reminiscent of ichthyosis.[4] At the peak of the response, this patient's apparent serum cholesterol was 254 mg per 100 ml. (initial level 328) triglyceride 212 (method of van Handel and Silversmit [7] and serum lipoproteins —S_f n 52 84 300 14 and 233 mg per 100 ml. respectively in classes of 70-400 40-70 25-40 20-25 and 1 10 urinary 17-ketosteroid output was 3 4 and hydroxycorticoid 4.5 mg per 24 hours whereas 3 weeks later 17 ketosteroid had apparently increased to 4.5 mg * Growth of hair on the scalp had fairly well recovered and growth of hair on the body resumed 4 months after treatment with triparanol was stopped. Slight loss of hair from the scalp and moderate loss of hair from the body occurred in Patient No. 6 and moderately severe loss from the scalp without loss from the body occurred in Patient No. 20 Patient No. 59 continued to take triparanol through an episode of thinning of the scalp hair with subsequent resumption of growth of the hair this may have been associated with her known hypothyroidism Resumption of growth of the hair in other patients began 3 to 4 months after treatment with triparanol was stopped.

*We are indebted for the ultracentrifugal serum analyses to Dr. Lena A. Lewis, and for the urinary assays to Dr. [illegible], both of the Cleveland Clinic Foundation

Comment

1 Serum cholesterol Mean apparent decrease in serum cholesterol is less in this series of patients than in the patients of many previous reports. This probably reflects the fact that the post treatment data were obtained after several months of treatment when a partial "rebound" from lower initial post-treatment levels is not infrequent

By the method of Abell and associates,[4] desmosterol gives about 60 per cent of the color developed by cholesterol and in patients treated with triparanol it accounts on the average for about 25 per cent of total serum sterol.[8] On this basis, net decrease in total serum sterol in this series of patients was about 7 per cent and the decrease in patients with initial serum cholesterol contents of 260 mg per 100 ml. or more was of the order of 15 to 18 per cent.

Table II Effect of triparanol on apparent serum cholesterol by age sex diagnostic group

Group Subgroup	Number of patients	Initial	Final	100 (final/initial)
IHD				
Men				
Age 30-50	24	279 4 ± 11	239 7 ± 6 7	85 3 ± 3 4
60-71	22	263 3 ± 14	222 6 ± 7 4	85 0 ± 4 3
Women				
Age 30-59	8	295 6	267 3	91 1
60-69	4	294 0	255 8	80 0
Diagnosis				
MI	21	276 7	231 4	85 3 ± 4 9
CI	24	285 9	250 8	89 9 ± 4 2
MI + CI	13	250 0	233 3	91 4 ± 2 7
IHD subtotal	58	276 5 ± 7 7	238 1 ± 5 0	8 0 ± 2 2
HC Men	7	296 4	264 3	89 1
Women	6	320 3	254 0	79 0
IHD + HC Total	71	282 1 ± 6 5	242 0 ± 4 5	87 3 ± 1.9

*Difference (initial-final) divided by standard error of difference is [illegible]

Pretreatment serum cholesterol content (means of [illegible], where numbers are sufficient, standard errors of means) final observations during treatment indicate apparent serum cholesterol content and per cent ratios of final initial levels.

Table III. Initial serum cholesterol and apparent response

Range (mg./100 ml.)	Number of patients	Apparent serum cholesterol means (mg./100 ml.) Initial	Final	100 (final/initial)
Less than 220	9	205.0	213.7	101.6
220-239	6	228.1	221.0	98.2
240-259	11	249.4	235.6	94.8 ± 4.2
260-279	9	271.3	233.5	85.2 ± 4.3
280-299	10	289.5	235.1	81.2 ± 2.[illegible]
300 and over	26	335.9	271.0	81.9 ± 2.7
Less than 260	26			98.8 ± 2.8
260 and over	45			82.2 ± 0.5

Response of apparent serum cholesterol [illegible] and by levels of pretreatment serum cholesterol [illegible]. Means of [illegible] groups and [illegible] of apparent final [illegible] initial [illegible] with standard error of means. [illegible] difference between groups under 260 and those 260 and over is 16.6 mg. per 100 ml.; standard error of difference is [illegible], and difference [illegible]. Standard deviations were [illegible] from values multiplied by [illegible] because of small groups.

Table IV. Clinical improvement during therapy in 7 of 25 CI patients

Number	Age (yr.)	Sex	Serum cholesterol (mg./100 ml.) Initial	Final	Cardiac [illegible] Angina	ECG	Month
12	56	M	273	237	+	0	5
19	46	M	315	233	+	+	8
20	41	M	336	233		+	13
22	61	M	262	227		+	6
31	60	M	273	237	+		14
56	41	M	227	192	+		6
58	66	M	233	230	+		7
Total					5	3	

As noted in the text, 2 patients showed signs of deterioration [illegible] during therapy.

Table V. Loss of hair during prolonged therapy with triparanol

Number	Age	Sex	Serum cholesterol (mg./100 ml.) Initial	Final	Month	Comment
5	57	M	328	232	7	Severe loss of scalp and body hair, skin change
6	38	M	352	290	12	Moderate loss of scalp and body hair only
7	56	M	332	261	8	Slight loss of scalp hair only
8	51	M	232	236	5	Slight loss of scalp hair only
31	57	M	332	291	12	Slight loss of scalp hair only
57	33	M	315	332	11	Slight loss of scalp hair only (regrew during ther[illegible]) (hypothyroid)
60	59	M	253	239	13	Moderate loss of scalp hair only

The greater decrease in patients with high pretreatment serum cholesterol has been noted by others; the relatively sharp apparent "cutoff" of the effectiveness of triparanol at levels less than 260 mg. per 100 ml. in this series probably reflects a chance distribution of data.* To some, from the aspect of establishing and maintaining an effective gradient between tissue and plasma sterol contents, triparanol, at least in the absence of severe hypercholesterolemia, seems to be no more, or perhaps less, effective than other means.[8] However, this inference requires support from tissue analyses, and does not bear on possible additive or synergistic properties of triparanol when used in association with other hypocholesterolemic measures.[9]

2. Ischemic heart disease. Subjective relief of angina in 5 of 25 patients with CI and angina was not so frequent as has been described in some earlier reports. Objective improvement was observed in 3 of 58 patients with IHD; each of these had CI, so that the objective improvement rate in the group with CI was 3 of 25 or about 10 per cent; these instances were balanced by 2 patients with CI who showed electrocardiographic signs of deterioration during treatment. It seems likely that such progressions might occur spontaneously in untreated patients observed over long periods of time. It was reassuring that no patient in this high-risk group suffered a myocardial infarct during treatment. However, neither the size of the group nor the duration of the observation permit any conclusion from this negative finding. Rather, as previously noted,[2] firm conclusions as to the effectiveness of this drug in cases of coronary atherosclerosis must await carefully planned longitudinal studies in a susceptible population group, which we understand are now being undertaken.

3. Loss of hair. Loss of hair was the only side effect observed; it occurred in 7 of 18 women. When this group is added to that of Achor and associates,[4] this side effect seems to be most common in women after the menopause (11 of 14 instances of loss of hair). For women in this age group loss of what St. Paul referred to as woman's "crowning glory" is so very disturbing as probably to be a contraindication to trial of this drug in the absence of severe hypercholesterolemia.

*Data from larger series indicate that responsiveness extends to initial serum levels of 200 mg. per 100 ml.

Summary and conclusions

1. In 71 office patients given triparanol for an average of 11 months, apparent serum cholesterol decreased by an average of about 10 per cent, and most commonly and significantly (average about 20 per cent) in patients with pretreatment serum contents of 260 mg. per 100 or more. Yet average actual changes in *total* serum sterol were probably about two thirds of the apparent changes, viz., 7 and 15 per cent, respectively.

2. Subjective improvement (anginal relief) occurred in 5 patients with anginal complaints, and electrocardiographic improvement in response to exercise was seen in 3 of 25 patients with coronary insufficiency; however, objective improvement in 3 was balanced by signs of deterioration in 2.

3. Loss of hair was observed in 7 postmenopausal women; loss of hair from the scalp was severe in 1, moderately severe in 2, and slight in 5; it was associated with loss of hair from the body in 2 and changes in the skin in 1. In 1 patient known to be hypothyroid, thinning of the hair began during triparanol treatment, and growth was resumed during continued treatment.

4. Triparanol is a moderately effective hypocholesterolemic agent which is most effective in patients with definite hypercholesterolemia (in excess of 259 mg. per 100 ml.). Its use should be restricted to these in view of possible side effects, notably loss of hair and, although only at much larger doses than those commonly used, diminished adrenal cortical responsiveness.

REFERENCES

1. Corcoran, A. C., Zimmerman, H. A., and Citarella, R.: Note on MER 29 in arteriosclerotic heart disease, Prog. Cardiovas. Dis. 2:576, 1960.
2. Corcoran, A. C.: Coronary atherosclerosis. Status of MER 29 (triparanol), Am. Heart J. 61:431, 1961.
3. Corcoran, A. C.: Letter to the Editor, Am. Heart J. 62:571, 1961.
4. Abell, L. L., Levy, B. B., Brodie, B. B., and Kendall, F. E.: A simplified method for the estimation of total cholesterol in serum and

demonstration of its specificity J Biol. Chem 195:357 1952.

5 Dimond, E. G The exercise electrocardiogram in office practice, Springfield Ill 1961 Charles C Thomas, Publisher

6. Achor R. W P Winklemann R. K., and Perry H P Cutaneous side effects from use of triparanol (MER 29) preliminary data on ichthyosis and loss of hair Proc. Staff Meet. Mayo Clin. 36:217 1961

7 Van Handel, E., and Silversmit D B Micromethod for the direct determination of serum triglycerides, J Lab. & Clin. Med 1:152 1957

8. Steinberg D Avigan, J and Feigelson E. B Effects of triparanol (MER 29) on cholesterol biosynthesis and on blood sterol levels in man, J Clin Invest. 40:884, 1961

9 Hollander W., Chobanian, A V., and Wilkins, R. W Separate and combined effects of cholesterol lowering agents in patients with and without coronary artery disease, Annual Meeting, American Medical Association, New York presented June 29 1961

Congenital heart disease with pulmonary ischemia
A study of the pulmonary vascular lesions before and after systemic pulmonary anastomosis

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The general interest in obstructive pulmonary hypertension secondary to left-to-right shunt in congenital heart disease, began shortly after Gross[1] treated patients who had patent ductus arteriosus by ligating the patent vessel. It was found later that patients with high pulmonary pressure died during or soon after operation because of right ventricular failure[2,3]—the defect had been acting as a safety valve by which the right ventricle was protected from high pressure in the pulmonary circulation.

The incidence of fatal pulmonary hypertension and the concomitant obstructive lesions in the pulmonary arteries, due to an artificial shunt between the systemic and pulmonary circulation, has been studied by Wagenvoort and co-workers[4] and Ross and associates.[5] Pulmonary vascular changes analogous to those seen in congenital heart disease with left-to-right shunt have been produced experimentally by creating such an artificial shunt.[6]

Although considerable work has been done in this field, the exact mechanism responsible for the vascular changes is not known. It has been suggested that the structural changes of the intima of the small arteries and arterioles develop in response to passive and hyperkinetic pulmonary hypertension and gradually obliterate the pulmonary vascular bed.[7] Another view postulates a congenital deficiency of the media of the small pulmonary arteries, which results in intimal fibroelastic thickening as a protective reaction which finally obstructs the vascular lumen.[8]

In an attempt to throw some light on the pathogenesis of the pulmonary vascular lesions in congenital heart disease, both in patients who have lung ischemia and in those who have had an artificial systemic pulmonary shunt, we have examined the histologic lesions in the vessels of infants and young children who suffer from the tetralogy of Fallot, tricuspid atresia, or pulmonary atresia. In evaluating the various morphologic pictures we have considered the effect of age and have introduced new standards and values intended to put the work on a sound basis. We have also compared the histologic appearances of the vessels of the lung on the same side as the anastomosis with those of the opposite lung as well as with those of normal control subjects, and we have related the lesions to the age at operation and the duration of the shunt.

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Table I Clinical and laboratory data of patients studied

Case number	Sex	Age	Auscultation	ECG	X-ray	Cause of death	Diagnosis at autopsy
1	F	2 mo	ESM SSS	RVH	HNE PO	HF	TF
2.	F	2 mo	ESM SSS	RVH	HE PP	On the operating table	TF
3	F	2½ mo	ESM SSS	RVH	HNE PO	HF	PA PDA
4	M	2½ mo	ESM SSS	LVH	HNE PO	HF	TA ASD VSD
5	M	3 mo	ESM SSS	LVH	HNE PO	HF	TA ASD VSD
6.	F	4 mo.	ESM SSS	RVH RAH	HE, PO	HF	PVS Inf stenosis
7	M	5 mo	GM SS(UND)	LVH	HE, PO	On the operating table	PA, TA
8	M	5 mo	ESM SSS	RVH	HNE PO	On the operating table	PVA Inf agenesis
9	F	5 mo	ESM SSS	Normal	Slight HE	On the operating table	TF
10	F	8 mo.	ESM WSSS	Dextro-cardia	HE PP	On the operating table	TF
11	M	11 mo.	ESM IDM	IRBBB	HE PO	Pneumonia	TF
12	F	1 yr	ESM PrM	RVH P-PL	HE PO	On the operating table	TF
13	M	1 yr	ESM SSS	RVH P-PL	HNE PO	After angiography	TF
14	F	13 mo	ESM SSS	RVH	HNE PO	HF	TF
15.	M	17 mo.	Not mentioned	BVH P-PL	HE PO	On the operating table	PVA ASD PDA
16	M	21 mo	ESM CM	HAV Dextro-cardia	HE, PO	HF	TF
17	M	3½ yr	ESM CM	RVH	HE PO	HF	TF
18.	F	8 yr	ESM SSS	RVH	HNE PO	On the operating table	TF

Key:
ESM Ejection systolic murmur
SSS Single second sound
GM Gibson's murmur
UND Undetermined
WSSS Wide split second sound
IDM Immediate diastolic murmur
PrM Presystolic murmur
CM Continuous murmur
RVH Right ventricular hypertrophy
LVH Left ventricular hypertrophy
RAH Right atrial hypertrophy
IRBBB Incomplete right bundle branch block
P-PL P-pulmonale
BVH Biventricular hypertrophy
HAV Hypertrophy of anterior ventricle
HNE: Heart not enlarged
PO Pulmonary oligemia
HE Heart enlargement
PP: Pulmonary plethora
PA Pulmonary atresia
PDA Patent ductus arteriosus
SS Second sound
TA Tricuspid atresia
ASD Atrial septal defect
VSD: Ventricular septal defect
PVA Pulmonary valve agenesis
TF: Tetralogy of Fallot
HF: Heart failure
Inf: Infundibular

Methods and material

The age of the patients ranged from 2 months to 8 years. Each had been investigated during his life and found to have congenital heart disease with oligemic lungs. Each had had a complete physical examination with roentgenogram of the chest and heart and electrocardiogram (Table I). A phonocardiogram was taken in 10 patients but none had had a cardiac catheterization. In all but 10 heart failure was established as the cause of death. Of

the 10 one died of pneumonia 7 died either on the operating table during an attempt to develop a systemic-pulmonary anastomosis or a few hours afterward and one died after angiography Seven patients underwent successful operations to create anastomoses, and had a postoperative survival time which varied from 3 days to 10 months (Table II) Postmortem examinations were performed on all and the available data are summarized in Table III Sections were taken from each lung slightly below the level of the hilum from the apex of the lower lobe in a plane at right angles to the main vessels so that they included both large and small vessels. All the sections were from tissues which had been fixed for at least 3 days in a solution of 10 per cent formalin and standard paraffin blocks were prepared. At least five serial sections at 25μ intervals to a total depth of approximately 300μ, were cut from each block. Each section was stained with Weigert's elastic stain counterstained with van Gieson's for collagen tissue and neutral red for nuclei The muscular arteries

Table II Data relating to operative procedure

Case number	*Age at first operation*	*Anastomosis*		*Age at death*	*Postoperative survival*
		First operation	*Age at second operation*		
1	8 wk.	Potts procedure, left	Not done	8 wk.	3 days
3.	10 wk.	Blalock, left	Not done	12 wk.	14 days
4	4 wk.	Blalock, left	10 wk.	10 wk.	6 wk.
5.	3 wk.	Blalock, left	3 mo.	3 mo.	10 wk.
14	3 mo.	Blalock, left	Not done	13 mo.	10 mo.
16.	16 mo.	Blalock, left	21 mo. pulmonary valvotomy	21 mo.	5 mo.
17	38 mo.	Blalock, left	Not done	42 mo.	4 mo.

Table III Postmortem data of the cases examined

Case number	*Age*	*Weight of heart (Gm.)*	*Thickness*		*Weight*		*Caliber of anastomosis*
			Right ventricle (cm.)	*Left ventricle (cm.)*	*Right lung (Gm.)*	*Left lung (Gm.)*	
1	8 wk.	28	—	—	40	40	2.0 mm.
2.	8 wk.	40	H	N	26	26	—
3	10 wk.	54	1.0	N	28	36	3.0 mm.
4	10 wk.	42	0.3	1.0	44	40	3.0 mm.
5.	3 mo.	54	0.1	1.2	46	44	Thr
6	4 mo.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
7	5 mo.	42	N.A.	N.A.	64	50	0.3 cm.
8.	5 mo.	70	1.5	1.5	65	59	N.A.
9	5 mo.	56	1.5	N.A.	52	48	0.3 cm.
10.	8 mo.	42	0.8	0.8	30	30	—
11	11 mo.	112	H	N	9	44	—
12.	11 mo.	70	0.8	0.8	55	50	N.A.
13	15 mo.	84	0.7	1.0	96	104	—
14	13 mo.	58	1.0	0.5	54	35	0.3 cm.
15	17 mo.	148	1.1	1.1	52	48	—
16	21 mo.	S.E.	N	H	62	60	N.A.
17	3½ yr.	190	0.8	1.0	90	80	0.5 cm.
18.	8 yr.	80	1.0	1.0	N.A.	N.A.	N.A.

Key to abbreviations Thr.—thrombosed; H—hypertrophied, N.A.—Not available; N—normal, S.E.—slightly enlarged.

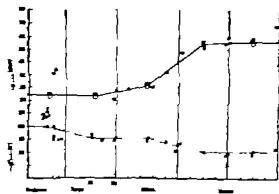


Fig. 1. The mean transitional diameter (*MTD*) and mean medial value (*MMV*) of pulmonary muscular arteries in 25 normal infants and children used as controls plotted as a function of age. MTD in microns. MMV as per cent of external diameter.

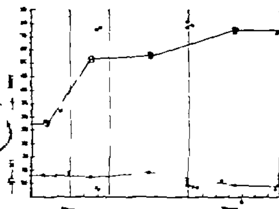


Fig. 2. The mean transitional diameter (*MTD*) and mean medial value (*MMV*) of pulmonary muscular arteries in 18 patients who had congenital heart disease with ischemic lungs plotted as a function of age. MTD in microns. MMV as per cent of external diameter.

were examined over an area of 2 square centimeters and their external diameter and the ratio of the thickness of the medial coat to the external diameter were recorded. A mean value was extracted in each section for both external diameter (MTD) and medial value (MMV). The ten with the minimal values were considered to be reasonable representatives of the mean values at the terminal portion of the muscular segment, i.e., the transitional region. We did not adopt the method of naming an artery according to its diameter[4] since we thought that it was unsatisfactory in a group of young patients, because of the considerable variance in the caliber of the lumen with age. According to our classification an artery with more than two distinct, complete elastic laminae in its wall regardless of its caliber has been called "elastic." The area of transition in which the elastic artery becomes muscular wherein there are only two complete elastic laminae together with a definite middle muscular layer is not considered in this study. On the other hand, the transitional zone between a muscular artery and an arteriole with its smaller diameter and thickness of the media, has been found to be particularly important. Although stable in pulmonary vessels of persons without congenital heart disease or pulmonary hypertension, it presents considerable variations in the various types of congenital heart disease associated with pulmonary plethora or oligemia.

The stillborn, full-term infant with no congenital heart disease has shown an MTD that ranges from 23 to 27μ and an MMV of 22 to 26 per cent. Soon after respiration starts in the newborn infant the same area is dislocated centrally to an MTD of 40 to 45μ, with an MMV of 15 to 20 per cent (Fig. 1). There is some thinning of the wall, yet the total quantity of the muscle tissue is not decreased but rather slightly increased. The arterioles, which in the fetus exhibit a considerable amount of muscle fibers but poor elastic tissue, expand as the muscular coat thins, so that there is a progressive development of the muscle and the elastic laminae. Thus, an arteriole which previously had

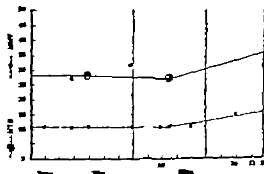


Fig. 3. The mean transitional diameter (*MTD*) and mean medial value (*MMV*) in pulmonary muscular arteries of 7 patients with congenital heart disease after a systemic-pulmonary anastomosis plotted as a function of duration of shunt. MTD in microns. MMV as per cent of external diameter.

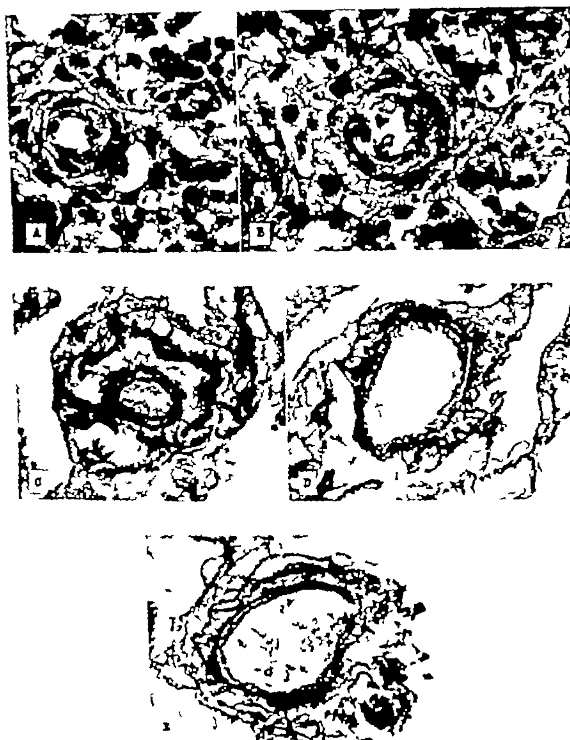


Fig. 4. *A*, A pulmonary arteriole in a stillborn infant used as a control. There is a considerably thickened muscular wall of approximately 33 per cent of the external diameter (28μ). *B*, From a 3-day-old infant, a pulmonary arteriole of the same size with thinner muscular wall (24 per cent) and a wider lumen. Poor elastic tissue is present (28μ). *C*, A terminal pulmonary artery from a 5-month-old infant. Note the thin muscular layer of 16 per cent thickness and the well-developed elastic tissue (23μ). *D*, Terminal pulmonary artery in 2-year-old child used as a control. The muscle shows thinner layer (9 per cent) and it has been centrally dislocated (50μ). *E*, Normal terminal pulmonary artery in a 3-year-old child. Medial thickness of only 6 per cent (55μ).

only one elastic ring may in a few months appear as a small but well-developed muscular artery with two clearly differentiated elastic laminae and a well-defined muscular layer (Fig 4)

Results

The available data on the 25 normal control subjects are summarized in Fig 1 It is apparent that the medial thickness, which is considerable in the stillborn full term infant (MMV of 20 to 25 per cent) rapidly declines to 10 to 15 per cent within a few months and this decline continues at a slower pace until the age of 4 years, when a slight rise appears. When we consider these values in the transitional zone of the muscular arteries we find them in sharp contrast the mean transitional diameter rises rapidly soon after the child begins to breathe (40 to 50μ) with a short decline which lasts until the age of approximately 1 month and a steady rise thereafter until it reaches between 60 and 80μ. It is assumed therefore that a relative increase in the muscular tissue takes place during the first month of life

In early infancy the ischemic lungs of the patients we studied showed no great difference in the over-all external diameter of the transitional pulmonary muscular vessels, but the medial coat was strikingly and consistently thin (MMV of 4 to 16 per cent) The small fluctuation in the values of medial thickness compares with the wide range of the transitional diameter (25 to 75μ) (Fig 2) Small muscular vessels (MTD of 25μ) have appeared in only 3 patients (Cases 2 8 and 10) and their muscular thickness was almost comparable to that seen in patients who have congenital heart disease with plethoric lungs.[9] The other patients have shown a minimal amount of middle muscular coat, that is to say a relative loss of muscle tissue (Fig 2) in striking contrast to the homolateral lungs of the surgically treated patients in whom the values tended to approach those of the normal controls (MMV of 10 to 15 per cent and MTD of 23 to 35μ) (Fig 3) i.e. the medial transitional zone was dislocated distally and the thickness appeared to be greater a relative gain of muscle tissue. There was no apparent correlation between the medial thickness and the size of the anastomosis or the postoperative survival time. No obstructive changes were observed which could be attributed to the increased flow of blood The MTD and MMV of the pulmonary arteries were found to be similar both in the lungs of the normal controls and in the lungs on the same side as the anastomosis. The slight degree of intimal proliferation found in the muscular pulmonary arteries (Cases 4 5 16 and 18) was not attributed to the shunt since it was found in both lungs (Figs. 6 and 8) but in Cases 3 8 9 12, and 14 there were widespread thromboses of the bronchial arteries on both sides (Figs. 5 and 6) There were a few similar thrombi in Cases 8 9 12 and 14 which differed widely in the degree of organization (Figs. 6 and 7) We found a slight fibroelastic thickening of the intima of the large elastic arteries in Cases 5 6 15 and 16 and a moderate degree in Case 18 (Fig 6) There was some venous thrombosis in Cases 4 12 and 18 (Figs 5 and 8) Furthermore Cases 8 and 18 exhibited multiple defects of the media of the middle sized arteries but the fibroelastic proliferation seemed to be entirely independent of these defects (Fig 8)

Discussion

The relative increase in the middle coat of the small pulmonary arteries on the same side as the anastomosis, as indicated by the low transitional zone of 23 to 35μ and high medial thickness of 10 to 15 per cent (Fig 3) is probably the result of a stimulus exerted by the increased flow of blood The size of the anastomosis was such as to suggest that the reduced circulation in the corresponding lung was corrected without excessive inflow of blood and the roentgenographic appearances confirmed the fact that the systemic pulmonary anastomosis was working efficiently That all patients who had a postoperative period which ranged from 3 days to 10 months were without obstructive lesions, such as are usually attributed to a shunt is an optimistic finding which indicates the importance of the size of an anastomosis capable of allowing a normal or nearly normal pulmonary flow Although a large shunt usually guarantees a dramatic improvement in the condition of the pa

tient, it is apt to initiate a secondary obstructive hypertension, which eventually proves fatal.[4,5] The relative loss of arterial muscle tissue in the opposite lung and in the lungs of patients not treated by operation and the fact that patients with successful anastomoses between the two circulatory systems tend to restore the media of the small pulmonary arteries to normal (Fig 3) are strong indications of the importance of



Fig 5 *A* Case 3 right lung A large bronchial artery markedly dilated and thrombosed half of the lumen is still patent (×370). *B* Case 3 left lung. A distal pulmonary muscular artery with an external diameter of 30μ and medial thickness of 15 per cent (×370). *C*, Case 4 Pulmonary artery showing intimal fibroelastic thickening (×370). *D* Case 4 The transitional zone from a pulmonary muscular artery to an arteriole with an external diameter of 30μ. *E*, Case 4. Wall of a vein with fibroelastic thickening projecting into the lumen (×370) *F* Case 4. Prominent venous tree compared with an elastic artery giving rise to muscular branch (×38).

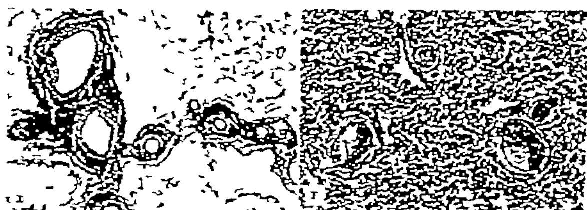


Fig. 6. *A*. Case 5, left lung. Terminal pulmonary artery of 40μ external diameter and 1[illegible] per cent medial thickness. *B*. Case 5, right lung. In the opposite lung of the same patient as in *A*, a distal artery of 8[illegible]μ diameter and 2[illegible] per cent medial thickness, showing slight but diffuse intimal proliferation. *C*. Case 8. Note the prominent bronchial arterial tree, and one small muscular artery branching off an arteriole (×100). *D*. Case 9. Large thrombus in a bronchial artery leaving a narrow crescent-shaped lumen (×370). *E*. Case 10. Prominent pulmonary arterial tree with thick media (×100). *F*. Case 12. Two bronchial arteries with organized and recanalized thrombi (×55). (For Fig. 6,*G*, see top of opposite page.)



Fig. 6*b*. Case 12. A very much dilated vein as compared to an elastic artery (×38).

Fig. 7. *A*. Case 14, right lung. Bronchial artery showing an organized thrombus (×370). *B*. Case 14, left lung. Pulmonary artery with an external diameter of 40μ and 14 per cent medial thickness. *C*. Case 16, left lung. Elastic artery showing internal fibroelastic thickening (×38). *D*. Case 16, left lung. Pulmonary arteries of 38μ diameter and 12 per cent medial thickness.



Fig. 8. *A*, Case 18, right lung. Pulmonary artery showing defects of the medial layer and ring-like intimal thickening which considerably reduces the lumen (×370). *B*, Case 18, left lung. A middle-sized muscular artery with intimal thickening on the right side, and considerable thinning of the opposite wall, probably representing defective development (×370). *C*, Case 18. Marked intimal proliferation and partial occlusion of the lumen in a small vein (×370).

the blood flow as the essential stimulus for the maintenance of the muscular tissue and its normal functions. The importance of evaluating the flow immediately after operation cannot be overstressed.

The mild obstructive lesions in the pulmonary arteries and veins of 7 of the 18 patients had no apparent association with the anastomosis; these lesions were also equally obvious in the patients with ischemic lungs. It has been suggested that a progressive thrombosis of the pulmonary arteries follows the increased viscosity which results from secondary polycythemia and reduction of the blood flow.[11] A direct relationship between the obstructive lesions and the age of the patient has also been postulated.[12]

The prominent bronchial arterial tree noted in 12 of the 18 patients, with thrombotic lesions in Cases 3, 8, 9, 12, and 14 (Figs. 5 and 6), has been regarded as a compensatory mechanism to facilitate the flow of blood into the oligemic lungs. The *thrombotic lesions in the bronchial arteries* are probably due to the combination of at least two factors, both of which result in sluggishness of the circulating blood: one is the already recognized secondary polycythemia which accompanies thrombosis of the pulmonary artery, and the other is the abnormal dilatation of the vessels, which are unable to accommodate such an increased collateral circulation. Although one would expect an increased rate of flow in these vessels because of the difference in pressures between the two circulations, the anomalous dilation of the vessel walls does *constitute an important predisposing factor* to the development of the thromboses.

Summary

In 18 infants and young children with congenital heart disease associated with pulmonary oligemia the condition of the middle muscular layer of the small pulmonary arteries has been evaluated and compared with that in the lungs of 25 normal control subjects and that in the lungs, homolateral to a systemic-pulmonary anastomosis, of 7 surgically treated patients Age duration of shunt, and size of anastomosis were taken into consideration in the evaluation of the results. In order to standardize the results the mean values of external diameter and medial thickness were calculated at the zone of transition between the arteries and the arterioles It was observed that the muscular tissue tended to revert to normal after a well judged systemic-pulmonary anastomosis. The possibility was suggested that the flow of blood is the important factor in maintaining the normal quantity and function of the muscular tissue. A relative loss of muscle in the arteries of the oligemic lungs was also observed and slight intimal thickening unrelated to the anastomosis. A possible cause of the prominent bronchial arterial tree with a high incidence of thrombosis is also suggested.

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REFERENCES

1 Gross, R. E.: Surgical management of patent ductus arteriosus, with summary of four surgically treated cases, Ann. Surg. 110:321 1939
2. Johnson, E. R., Wermer P., Kuhner M and Cournand, A. Intermittent reversal flow in a case of patent ductus arteriosus A physiologic study with autopsy findings, Circulation 1:1293 1950
3 Swan, H Trapnell, J M., and Denst. J Congenital mitral stenosis and systemic right ventricle with associated pulmonary vascular changes frustrating surgical repair of patent ductus arteriosus and coarctation of aorta Am. Heart J 38:914, 1949
4. WagenVoort C A., DuShane, J W and Edwards, J E. Cardiac Clinics No. 151 hypertensive pulmonary arterial lesions as a late result of anastomosis of systemic and pulmonary circulations, Proc Staff Meet Mayo Clin. 35 186, 1960.
5 Ross, R S., Taussig H B and Evans M H Late hemodynamic complications of anastomotic surgery for treatment of tetralogy of Fallot, Circulation 18:553 1958
6. Heath, D Donald, D E., and Edwards, J E Pulmonary vascular changes in a dog after aorto-pulmonary anastomosis for four years, Brit Heart J 21 187 1959
7 Wood, P Diseases of the heart and circulation, London, 1956, Eyre & Spottiswoode, p 838.
8. Evans, W Congenital pulmonary hypertension, Proc Roy Soc Med. 44:600 1951
9 Brenner O Classification of pulmonary arteries, Arch. Int. Med 56:211 457 724 975 and 1189 1935
10 WagenVoort, C. A Neufeld, H N DuShane, J W and Edwards J E The pulmonary arterial tree in ventricular septal defect, Circulation 23 740 1961
11 Rich A. R A hitherto unrecognized tendency to the development of widespread pulmonary vascular obstruction in patients with congenital pulmonary stenosis (tetralogy of Fallot) Bull Johns Hopkins Hosp 82:389 1948
12 Heath, D DuShane, J W Wood E H and Edwards J E The etiology of pulmonary thrombosis in cyanotic congenital heart disease with pulmonary stenosis, Thorax 13:213 1958

Experimental and laboratory reports

Activation of subendocardial Purkinje fibers and muscle fibers of the left septal surface before and after left bundle branch block

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The fact that the Purkinje system plays a role in determining the normal sequence of activation of the mammalian ventricles is generally accepted. There is, however, some disagreement concerning the extent to which activity in Purkinje fibers influences the activation of the homolateral septal surface in the presence of experimental bundle branch block (BBB). A similar question exists with respect to the sequence of activation of the homolateral septal endocardial muscle fibers. Sodi-Pallares[1] has concluded that, with left bundle branch block (LBBB), after the wave of excitation arrives at the left Purkinje network, "it proceeds to activate the left septal surface in a normal sequence and direction without any significant delay." Erickson[2] has arrived at a somewhat different conclusion; he finds that the septum on the blocked side is activated in an orderly fashion from the contralateral ventricle and that "the homolateral septal endocardium has no intrinsic spread." Since it is generally agreed that the conduction velocity is considerably higher in Purkinje fibers than in ventricular muscle fibers,[3] this statement would appear to preclude any participation of the subendocardial Purkinje network in activation of the homolateral subendocardial septal muscle. A third possibility, suggested by the experiments of Burchell,[4] is that the direction of the excitatory pathways is determined by the predominant direction of the muscle fibers.

Recently, Medrano[5] has recorded action potentials from subendocardial Purkinje fibers at single sites on the right and left septal surfaces of canine hearts; the results of studies made prior to and after production of LBBB are in general agreement with the findings of Sodi-Pallares.[1] However, to demonstrate conclusively the sequence of activation of the surface of the interventricular septum, the time of onset of activity must be determined at multiple locations over the entire surface. Moreover, to relate this sequence to propagation in the subendocardial Purkinje system, electrical activity of Purkinje fibers also must be recorded from a large proportion of the selected septal sites. All previous studies[1,2,4,5] have failed to satisfy one or the other of these criteria.

By use of total cardiopulmonary bypass

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it is possible to apply close bipolar electrodes to any number of selected points on either septal surface through a ventriculotomy[4,7] and to record local activity both in Purkinje fibers and muscle fibers.[8,9] This technique has been used in the present investigation to study the effect of LBBB on the sequence of activation of homolateral subendocardial Purkinje fibers and muscle fibers in the canine heart *in situ*. In addition to the specific problem of activation of homolateral tissues during LBBB, these experiments are related to the general question of whether or not activity spreads from muscle fibers to Purkinje fibers. Experiments have shown conclusively that conduction from muscle to Purkinje fibers does take place in isolated preparations of canine heart[10]; however, there is still some doubt concerning the likelihood and extent of similar spread in the heart in situ.[11]

In this paper evidence is presented to show that, both before and after LBBB, local activation of muscle fibers of the left septal surface is preceded by activation of subendocardial Purkinje fibers.

Methods

A. Perfusion preparation. Adult mongrel dogs which weighed between 20 and 25 kilograms were anesthetized with thiopental sodium and placed on a Jefferson respirator which supplied both positive and negative pressure. Exposure of the heart and venae cavae was obtained through a transsternal incision in the sixth intercostal space. After the intravenous administration of heparin (2.5 mg. per kilogram), venous catheters were inserted through the azygos vein into the superior vena cava and through the right atrium into the inferior vena cava; an arterial cannula was inserted into the right femoral artery. Blood drained by gravity from the venae cavae into a rotating disc oxygenator, where it was equilibrated with a mixture of 95 per cent oxygen and 5 per cent carbon dioxide. From the oxygenator blood passed through two bubble traps and was returned to the animal by an occlusive roller pump via the femoral artery. Total cardiopulmonary bypass was effected by tightening tapes about the superior and inferior venae cavae. Arterial pressure was monitored continuously from the left femoral artery with a Statham pressure transducer. During total bypass, pump flow rates ranged between 70 and 90 c.c. per kilogram per minute; mean arterial pressure ranged between 90 and 100 mm. Hg.

A Brown-Harrison heat exchanger was incorporated in the arterial inflow line; the temperature within the left ventricular cavity was monitored with a thermistor and was maintained between 99 and 100°F.

B. Recording techniques. Plastic plaques which measured 0.5 cm. by 1 cm. and contained 3 to 5 silver contacts on one surface were sutured to the epicardial surfaces of the right atrium near the sinoatrial node, the left atrial appendage, and the right and left ventricles. Bipolar electrograms recorded through these electrodes served as reference points with respect to time during the cardiac cycle. The left surface of the interventricular septum was exposed through an anterior longitudinal incision which extended from the apex to the base of the

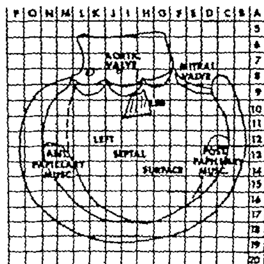


Fig. 1. Diagram of the septal surface of the left ventricle. Lines A-P and lines 5-20 form a reference grid. These lines were used in conjunction with the anatomic landmarks afforded by the aortic and mitral valves and anterior and posterior papillary muscles to position the exploring electrode accurately and reproducibly at the same 21 recording sites before and after left bundle branch block. *LBB* in the diagram represents the [illegible] portion of the left bundle branch up to the point of origin of the anterior and posterior false tendons. In the text and in subsequent figures, each position of the exploring electrode is defined in terms of the reference grid.

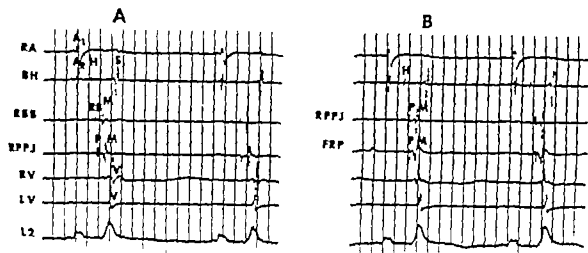


Fig. 2. Bipolar electrograms recorded from all the major subdivisions of the specialized conducting system of the right ventricle (RSCS). Part *A* shows electrograms recorded through electrodes positioned on the epicardial surface of the right atrium (*RA*), over the bundle of His (*BH*), the right bundle branch (*RBB*), the right Purkinje-papillary junction of the anterior papillary muscle (*RPPJ*), and on the epicardial surface of the right ventricle (*RV*) and left ventricle (*LV*). Lead II of a standard electrocardiogram is shown as the bottom tracing (seventh line) on the figure and is designated *L2*. The components of the electrograms in the first six lines are labeled as follows: *A*, right atrium near the sinoauricular node; A_1, right atrium recorded through the electrodes on the bundle of His; *H*, bundle of His; *S*, septum recorded through the electrodes on the bundle of His; *RB*, right bundle; *M*, action potential from adjacent muscle fibers; *P*, Purkinje-fiber activity at the RPPJ; and *V*, action potentials recorded from the epicardial surface of the right and left ventricles. Part *B* shows electrograms recorded from electrodes positioned as in *A*, except in the third line, where an electrode is positioned on the RPPJ, and in the fourth line, where an electrode is positioned midway on the FRP (free-running Purkinje fiber) as it courses from the base of the right anterior papillary muscle to the endocardial surface of the right ventricular wall. As in *A*, *P* indicates activity in Purkinje fibers, and *M* indicates activity in muscle fibers. In both *A* and *B*, note the sequential activation demonstrated by the electrograms recorded from indicated points *as the impulse spreads from the RA, through the SCS, and to the epicardial surface of the right ventricle.* The temporal relationship of each of these complexes can be related to the conventional Lead II electrocardiogram shown in the seventh line. Time lines in this and subsequent records are at intervals of 40 msec. Rapid components of complexes in this and subsequent figures have been retouched to ensure clarity in photographic reproduction.

heart. The incision was placed midway between the anterior descending branch of the left coronary artery and the major anterior branch of the circumflex artery; arterial bleeders were ligated individually. Close bipolar electrograms were recorded from multiple selected points on the septal surface through electrodes located in the tip of a plastic probe which was positioned manually and located with respect to anatomic landmarks within the ventricle and a grid of rectangular coordinates superimposed on a drawing of the left septal surface (Fig. 1). Use of these electrodes has been described for both acute[9,10] and chronic[11] experiments.

In the present series of experiments the exploring probe contained 3 leads and had 3 silver contacts at the tip. The contacts were arranged in the form of a triangle which measured 0.5 to 1.0 mm. on each side, and 2 bipolar electrograms were recorded from each location on the septal surface. The different orientation of the 2 sets of contacts employed at each location increased the likelihood of recording clear deflections from both Purkinje fibers and muscle fibers. Records from the exploring electrode, the fixed epicardial reference electrodes, and a standard Lead II electrocardiogram were photographed from an 8-trace switched-beam oscilloscope on 5-inch paper moving at 200 mm. per second. The reproducibility of such electrograms has been discussed previously.[9,11]

Bipolar electrograms were recorded from the same 21 points on the left septal surface in 8 complete experiments before and after complete LBBB was produced. LBBB was created by dividing the left bundle branch with a curved incision high on the septum below the point at which the bundle

emerges beneath the right coronary and noncoronary cusps of the aortic valve. Criteria for the adequacy of block were based on changes in the standard electrocardiogram and on delay of the activation of the septal surface; these criteria are described in detail in the subsequent section (Results).

Low frequency components of all records except Lead II were attenuated to increase base-line stability and facilitate identification of electrical activity in subendocardial Purkinje fibers.[8,9] Local activation time was taken as the peak of monophasic electrogram complexes or, with diphasic complexes, the instant at which the intrinsic deflection crossed the line of zero potential. A number of complexes were measured for each site and the average value was used in all determinations. The difference in time of activation obtained from a series of sequential complexes at a given location was less than 2 milliseconds. The results presented are based on some 4,000 measurements.

Results

I. Records and nomenclature. In order to facilitate the orderly presentation of data obtained in direct studies of each part of the specialized conducting system in situ, it is necessary to employ a nomenclature which readily identifies each component of each electrogram. The system which we have developed[7,8,9,12] has not previously been presented in detail. In Fig. 2, *A* and *B* show bipolar electrograms from the major subdivisions of the specialized conducting system of the right and left ventricles and a simultaneous Lead II electrocardiogram. The electrogram in the first line is recorded from the right atrium (*RA*) near the sinus node, and its major deflection is designated A_1. The three complexes in the second line represent activity beneath the electrode on the bundle of His (*BH*). The first complex results from atrial depolarization (A_2), the second from activity in the bundle of His (*H*), and the third from activity in the upper part of the interventricular septum (*S*). The third line shows an electro-

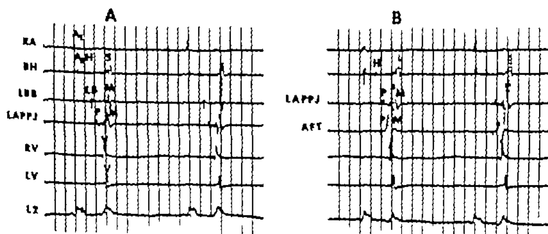


Fig. 3. Bipolar electrograms recorded from all the major subdivisions of the specialized conducting system of the left ventricle (LSCS). The third line of Part A is an electrogram which was recorded through an electrode positioned on the left bundle branch (*LBB*) just below the aortic cusps, and the fourth line is one from an electrode positioned on the left anterior Purkinje-papillary muscle junction (*LAPPJ*). The first complex of the electrogram recorded in the third line is designated *LB* (left bundle). The remainder of the nomenclature is as in Fig. 2; other electrodes are positioned as in Fig. 2. Electrograms recorded from peripheral Purkinje fibers of the left septal surface are shown in Figs. 4 and 5. Part *B* shows electrograms recorded through electrodes positioned as in *A*, except in the third line, where an electrode is positioned on the LAPPJ, and the fourth line, where an electrode is positioned on the anterior false tendon (*AFT*) which runs from the left septal surface to the left anterior papillary muscle. The remainder of the nomenclature is as in Fig. 2. In both *A* and *B* note the orderly sequence of activation demonstrated by the electrograms in the first six lines as depolarization spread from the right atrium, through the SCS, and to the epicardial surface of the left ventricle. The temporal relationship of each of these complexes can be related to the conventional Lead II electrocardiogram shown in the seventh line.

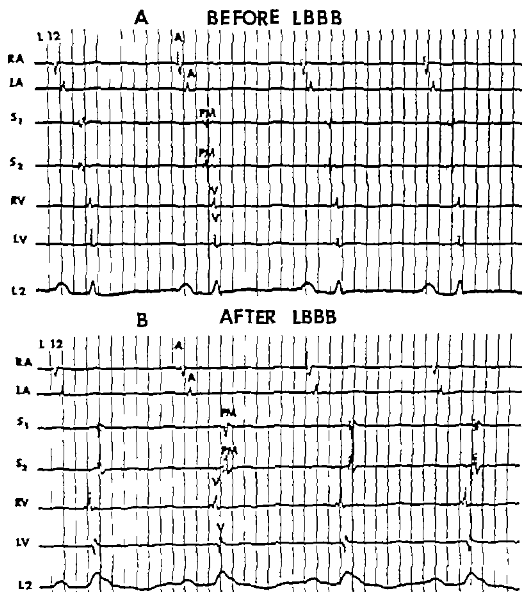


Fig. 4. Electrograms recorded through electrodes on the RA, LA (left atrium), RV, and LV, and electrograms S_1, S_2 recorded through the exploring electrode positioned at L 12 on the left septal *surface before (A) and after (B) surgical production of LBBB* at the level of line 11, which is proximal to the recording site (see Fig. 1). A standard Lead II electrocardiogram is shown in the seventh line. After LBBB (*B*) note that the RA to S_1, S_2 and RA to LV intervals have increased, the V complex *in the sixth line is altered in configuration, and the QRS complex in L2 is prolonged*, and that the RA to RV interval is not changed. The point of block is proximal to the recording site at L-12 on the standard grid diagram. Both before and after LBBB the P complex precedes the M complex *recorded through the exploring electrode positioned at L-12 on the left septal surface.* Note, however, that the P-M interval has become shortened after LBBB. The changes shown here in S_1 and S_2 should be contrasted with the tracings (S_1 and S_2) recorded at L 10 (above the level of block) *in Figs. 3A and 3B*.

gram from the right bundle branch (*RBB*) recorded through an electrode located approximately 2.5 cm. distal to the electrode on the bundle of His. At this site the electrogram shows two discrete complexes: the first (*RB*) represents activity in the Purkinje fibers of the right bundle branch and the second (*M*) results from depolarization of adjacent septal muscle fibers. In the fourth line the record from the right Purkinje-papillary junction (*RPPJ*) on the anterior papillary muscle also shows

two complexes the first represents depolarization of Purkinje fibers (*P*) and the subsequent deflections result from activity in adjacent papillary muscle fibers (*M*) The fifth and sixth lines show electrograms (*V*) recorded from the epicardial surfaces of the right ventricle (*RV*) and left ventricle (*LV*) The seventh line is a Lead II electrocardiogram the configuration of this tracing in each record is influenced by the combined effects of thoracotomy right and left ventriculotomy and position of the heart during recording procedures (compare Figs. 2 and 3) In the fourth line of Fig 2,*B* a record has been obtained from the free-running Purkinje fibers (*FRP*) midway between the RPPJ and the endocardial surface of the free wall of the right ventricle. As above the first complex (*P*) indicates activity in the Purkinje fibers, and subsequent activity (*M*) results from depolarization of muscle fibers.

In Fig 3 *A* and *B* show a similar set of records obtained from the specialized conducting system of the left ventricle and includes electrograms from the left bundle branch (*LBB*) the free-running Purkinje fibers in the left anterior false tendon (*AFT*) and the left anterior Purkinje-papillary junction (*LAPPJ*) Although not shown, records from the left posterior Purkinje-papillary junction are designated *LPPPJ* and those from the posterior false tendon as *PFT* The third line of Fig 3,*A* shows complexes recorded from Purkinje fibers in the left bundle branch (*LB*) immediately beneath the aortic cusps and from adjacent septal muscle fibers (*M*) The fourth line shows a record from the LAPPJ the first complex (*P*) results from depolarization of Purkinje fibers and the second (*M*) from activity in muscle fibers of the left anterior papillary muscle The fourth line of Fig 3,*B* shows activity recorded from the AFT discrete complexes resulting from activity in Purkinje fibers (*P*) and muscle fibers (*M*) are present Electrograms from the peripheral Purkinje system are shown in Figs. 4 and 5 This system of nomenclature is presented in Table I

The records shown in Figs. 2 and 3 were recorded from the same animal within a short period of time and present an opportunity to relate the activation of the major subdivisions of the specialized conducting system to each other and the over-all pattern of activation to the electrocardiogram It should be pointed out that the exact time of occurrence of each complex is dependent on the exact location of the recording electrode on the specialized conducting system. Thus the BH electrogram always appears during the first half of the P-R interval but may be somewhat earlier or later depending upon whether the re-

*Table I Suggested nomenclature to be used in studies of the specialized conducting system of the heart**

SCS	Specialized conducting system
A	Right atrium near the sinoatrial node
A	Right atrium recorded from beneath the bundle-of His electrode
A_x	Other right and left atrial points as indicated
V	Ventricle right or left as indicated
SA	Sinoatricular node
BH	Bundle of His
AV	Atrioventricular node
RBB	Right bundle branch
RPPJ	Right Purkinje-papillary junction
FRP	Free-running Purkinje fibers
LBB	Left bundle branch
AFT	Anterior false tendon of left ventricle
PFT	Posterior false tendon of left ventricle
LAPPJ	Left anterior Purkinje-papillary junction
LPPPJ	Left posterior Purkinje-papillary junction
M	Muscle at points as indicated
P	Purkinje fibers at points as indicated

*Based on abbreviations for each of the anatomic points from which electrical potentials are recorded.

cording electrode is located over the upper or lower part of the common bundle. The same situation is true with respect to the right bundle branch since this segment of the specialized conducting system usually *runs for 2.5 to 3 cm. beneath the endocardium of the right septal surface.* However, since conduction velocity in this structure is 2 to 3 times that found in the bundle of His,[7] the effect of electrode position on the temporal relationships of the RB complex to the ECG is less critical than in the case of the BH. The complexes recorded from the LB and from the PPJ of

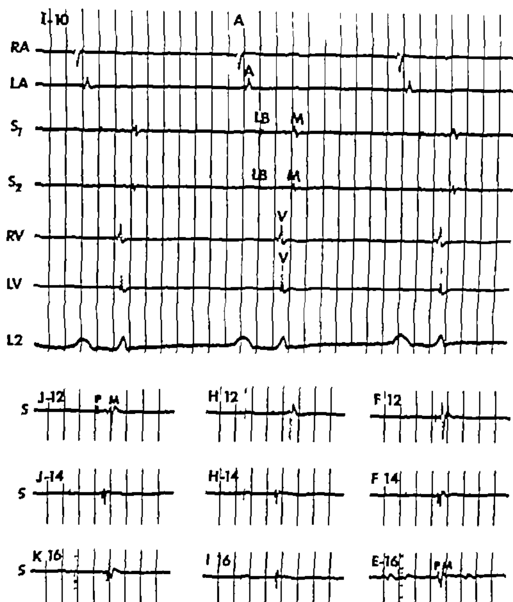


Fig. 54. A set of records obtained before LBBB through electrodes positioned on the RA, LA, RV, and LV, and through an exploring electrode positioned at *I 10* over the left bundle (*LB*) on the left septal surface. Also shown are single representative electrograms from 9 (*J 12* through *E 16*) of the remaining 20 recording sites. The point taken for zero reference time (right atrial electrogram) is indicated by a dashed line in each electrogram. Note that the Purkinje-fiber activity recorded over the left bundle precedes that of the underlying muscle by an interval of 80 msec.; at most recording sites progressively closer to the apex (rows 12, 14, and 16) the interval between the P and M complexes becomes shorter. At some peripheral points the interval is so short as to make separate identification difficult.

either the right or left ventricle are not subject to variation of the same magnitude because these recording sites are sharply localized anatomically. When records are obtained from free-running Purkinje fibers (FRP) in the right ventricle or from the false tendons (FT) in the left ventricle both electrode position and interelectrode distance should be known.

II. Normal activation of the left septal surface. During total cardiopulmonary by-pass a bipolar exploring electrode was used in previous studies to record from subendocardial Purkinje fibers on the left

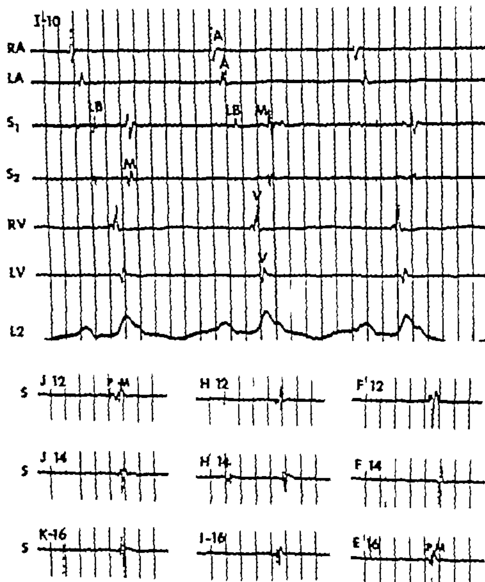
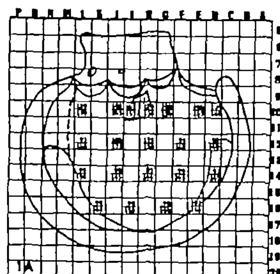
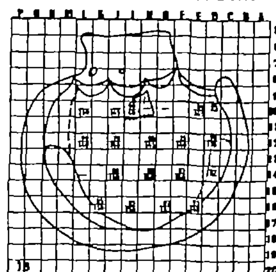


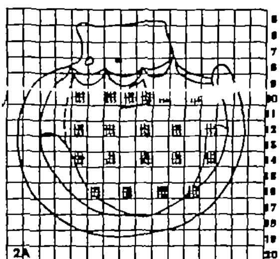
Fig. 5B. A set of records obtained after LBBB through electrodes positioned on the RA, LA, RV and LV and through an exploring electrode positioned at I-10 over the left bundle (*LB*) on the left septal surface. Also shown are single representative electrograms from 9 (*J-12* through *E-16*) of the remaining 20 recording sites. The point taken for zero reference time (right ventral electrogram) is indicated by a dashed line in each electrogram. Note that P complexes were recorded from the same sites at which they had been recorded before LBBB (Fig. 5A). P complexes recorded from the LBB above the level of transection (I-10) were not delayed after LBBB, all points below the level of LBB transection were delayed. At many recording sites the interval between the P and M complexes was reduced after LBBB.

SEPTAL MYOCARDIUM

SEPTAL PURKINJE NETWORK







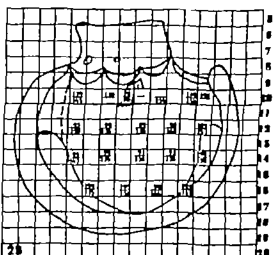


Fig. 6. Activation of the left interventricular septal surface (*1A*, *2A*) and of the subendocardial Purkinje fibers (*1B*, *2B*) before and after LBBB in 2 animals. Numbers at each point on the standard grid diagram represent the interval, in milliseconds, between activity recorded through the reference electrode on the right atrium and activation of the surface muscle fibers (*1A*, *2A*) or Purkinje fibers (*1B*, *2B*) at that recording site. Numbers above the line at each point were obtained before LBBB and those below the line after LBBB. Note that early activation of Purkinje fibers persisted at I 10 after LBBB since this point was above the level of section of the LBB; activity at all other recording points was delayed after LBBB. At many sites the P-M interval was decreased after LBBB; this can be seen if the value at a specific point in *B* is subtracted from the corresponding value in *A*.

septal surface[11] and to study the sequence of surface activation of the septal muscle.[6] In the present investigation detailed maps of the sequence of activation of both Purkinje and muscle fibers have been made simultaneously in order to study the temporal relationships between activity in each type of tissue and to compare the normal relationship with that found after left bundle branch block. The same 21 point on the left septal surface were selected for study in each animal. An electrogram from each of these points was recorded simultaneously with a Lead II electrocardiogram and with bipolar electrograms from the right and left atria and the epicardial surfaces of the right and left ventricles (Figs. 4,*A* and 5*A*). As has been shown pre-

viously [3,11] at most sites on the left septal surface the bipolar electrogram reveals 2 discrete components The first results from depolarization of local Purkinje fibers (P) and the second from local activity in septal muscle fibers (M) In order to increase the likelihood of recording both components and to facilitate identification of the Purkinje (P) complex, the 3 contacts in the exploring electrode were used to form 2 sets of bipolar leads thus 2 electrograms (S_1 S_2) were recorded from each site (Figs 4 and 5) The time of activation of Purkinje fibers and muscle fibers at each point was determined by measurement of the interval in milliseconds between activity at the reference electrode on the right atrium and that at the septal site The electrogram recorded from the right atrium always was a sharp complex of short duration and provided a distinct reference point in the cardiac cycle Throughout all experiments there was a constant temporal relationship between the right atrial electrogram the P wave of the electrocardiogram and the right ventricular electrogram therefore it was not necessary to consider changes in the location of the atrial pacemaker or in atrioventricular nodal transmission in the evaluation of the time of septal activation The QRS complex of the electrocardiogram was not employed as a reference point because of possible changes in configuration resulting from thoracotomy ventriculotomy and alterations in the position of the heart

Fig 5A shows one set of records (S S_2) obtained when the exploring electrode was positioned over the LBB (*I 10*) and single representative electrograms from 9 (*J 1?* through *E 16*) of the remaining 20 recording sites. In each of these latter records the zero reference time (right atrial electrogram) is indicated by the dashed line The P and M complexes can be identified in most of these records. High on the interventricular septum over the point of emergence of the left bundle branch activity in Purkinje fibers precedes that in underlying muscle by an interval which ranges from 75 to 85 msec (see also Fig 6) At recording sites progressively closer to the apex (rows 12, 14 and 16) the interval between the P and M complexes becomes shorter in most instances (Figs. 5A and 6) At some peripheral points the interval between the 2 complexes is so short as to make their separate identification difficult

After excitation of the Purkinje fibers of the LBB activity in the subendocardial Purkinje fibers of the septal surface is first recorded in the central portion of the septum (Figs. 5A and 6) This activity appears 65 to 80 msec after the right atrial electrogram In the areas of the septum activated latest the P complex appears 30 to 50 msec after that recorded from the central septum The latest activity in Purkinje fibers is recorded from fibers located at the base of the septum beneath the aortic and mitral annulae In each heart studied a clear P complex was demonstrated at from 16 to 21 of the 21 selected recording sites. In all but one instance failure to record a P complex was encountered in row 10 at the base of the septum This result is to be expected from anatomic studies of the canine heart [16] As can be seen in Fig 7 subendocardial Purkinje fibers are clearly demonstrated in iodine-stained specimens of the left septal surface at all locations except over the base of the septum beneath the aortic and mitral valves. The same figure also shows differences in the relative density of stained Purkinje fibers at other locations. The time required for activity to spread from the LBB throughout the subendocardial Purkinje fibers of the entire left septal surface ranged from 35 to 60 msec however the major part of the Purkinje system was activated within 23 to 28 msec

As described previously [?] under normal conditions, activation of the muscle fibers of the left septal surface generally is recorded first in a central area of the septum (Figs. 5 and 6) Adjacent to the anterior apical and posterior septal margins, depolarization of muscle fibers is completed within 12 to 20 msec after the earliest activity recorded in the central area Depolarization at the base of the septum appears later and the latest activity of muscle fibers on the septal surface is recorded immediately beneath the aortic annulus In these experiments, earliest activity of septal muscle fibers appeared between 80 and 100 msec [illegible] the atrial reference electrogram and the latest ac-



Fig 7 The specialized conducting system of the left septal surface and of the left ventricular wall stained with tincture of iodine (4 per cent). The LBB first presents beneath the endocardial surface of the left septum at the junction of the noncoronary and right coronary aortic cusps. The LBB then divides into many subdivisions and is distributed beneath the endocardial surface of the left septum and of the wall of the left ventricle. Two larger groups of fibers, the false tendons, extend to the anterior and posterior papillary muscles of the left ventricular wall. Note the absence of stained Purkinje fibers at the base of the septum.

tivity was recorded 140 to 150 msec. after the reference electrogram The time required for activation of the muscle fibers of the entire septal surface thus varies from 50 to 60 msec. If the peripheral parts of the septum beneath the mitral and aortic annulae are omitted from consideration the time required for activation of the remaining portions of the septal surface varies from 17 to 32 msec.

In these experiments as in previous studies[4] there was considerable variation from dog to dog in the exact sequence of activation of the septal surface (see Figs. 6 and 8) However in each heart there was a close correspondence between the sequence of activation of the subendocardial Purkinje fibers and the muscle fibers of the septal surface This is shown in the electrograms of Fig 5 and the data in Fig 6

III Activation of the left septal surface after LBBB After the normal activation pattern of the left septal surface had been determined the LBB was sectioned at line 11 between lines G and J in the standard grid diagram (Fig 1) Representative changes recorded after LBBB are shown in Figs. 4,B and 5B Activation of Purkinje fibers and of muscle fibers of the septal surface distal to the section was delayed (S_1 and S_2 in Fig 4,B see also Fig 5B) and the LV electrogram was delayed in the cardiac cycle and usually showed some change in configuration Also the QRS

complex of the Lead II electrocardiogram was widened the Q wave, when present under control conditions disappeared and the T wave showed changes compatible with BBB In all experiments selected for study LBBB was considered complete because there was delayed activation of muscle fibers at all points on the septal surface and delayed depolarization of Purkinje fibers at all sites from which P complexes were recorded distal to the incision. QRS duration was not employed as a criterion of BBB because of the experimental variations in this complex which have been discussed in Section I

After division of the LBB P complexes were recorded from most of the sites at which they had been found prior to block (Figs. 4,*B* 5*B* and 6) and also from several points at which they had not been recorded previously (Fig 6) The P complexes recorded from the LBB above the level of transection (I 10) were not delayed after LBBB (Figs. 5*A* and 5*B*) below the transection there was uniform delay of P complexes (Figs. 4,*B* and 5*B*) The earliest points of activity of the Purkinje system distal to the block were recorded in the central septum in only one experiment In most instances the earliest P complexes were recorded at multiple points from the anterior apical or posterior margins of the septum (Fig 6) P complexes recorded from the base of the septum after LBBB appeared relatively late in the cardiac cycle. After LBBB earliest P complexes distal to the block were delayed by 42 to 70 msec. however the time required for activation of the subendocardial Purkinje fibers at all sites at which P complexes

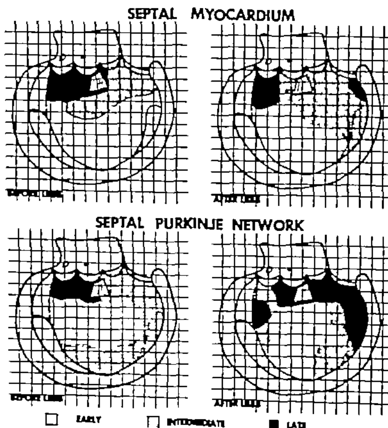


Fig. 8 An example of the activation pattern of Purkinje fibers and of muscle fibers beneath the endocardial surface of the left septum in the same heart before and after LBBB. The interval of time between earliest and latest activation was divided in thirds, both for Purkinje and muscle fibers; these intervals were designated early intermedia and late. See text for discussion

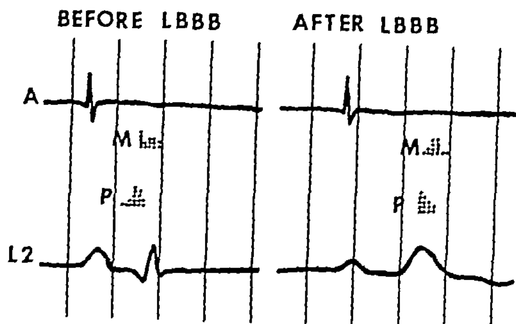


Fig. 9. A tracing of the atrial electrogram and Lead II electrocardiogram relating the times of activation of Purkinje and muscle fibers of the left septal surface to these records before and after LBBB in one experiment. Each dot shows the time of activation of the Purkinje (P) or muscle (M) fibers at one site on the left septal surface. Note the temporal relationship of the P and M complexes to the right atrial electrogram, the P-R interval, and the QRS complex before and after LBBB. The earliest Purkinje activation occurs at the same relatively early time both before and after LBBB, since the level of section of the LBB is distal to that specific recording site. Time lines are at intervals of 80 msec.

were recorded was reduced to 18 to 25 msec., or approximately one half of the control value of 50 to 60 msec. The time required for the activation of the muscle fibers of the septal surface was similarly reduced (Fig. 6). In addition to the fact that P complexes were recorded from most points after LBBB, it is important to note that at each of these sites the P complex preceded the M complex. Also, after LBBB at many recording sites the interval between the P and M complexes was reduced (Figs. 5B and 6).

II. Relationship of activation of the left septal surface to the ECG. The contribution from activity of the interventricular septum to the electrocardiogram has been considered in a number of papers[illegible] and is not one of the major objectives of the present investigation. Nevertheless, the data obtained in these studies have some bearing on this problem. As has been shown previously,[illegible] earliest activity of muscle fibers on the left septal surface is recorded in the central region and latest activity is found at the base (Figs. 5B and 6). Although there is some variation between individual hearts (Fig. 6), if the total time required for depolarization to involve the entire left septal surface is divided into 3 periods of equal duration, the spread of activity proceeds from apex to base (Fig. 8). Also, there is a close correspondence between the pattern of activation of the subendocardial Purkinje fibers and that of the septal muscle fibers (Fig. 8). Moreover, when the time of the P complex and the M complex recorded from each site on the left septal surface is plotted in relation to the Lead II electrocardiogram (Fig. 9), several conclusions appear to be justified. First, as would be expected, activity is recorded from the LBB and from Purkinje fibers before the initial deflection of the QRS. However, although activity in Purkinje fibers is not recorded after the first part of the upstroke of the R in Lead II, depolarization of muscle fibers of the septal surface takes place throughout the QRS complex and even as late as the termination of the S wave in Lead II.

After complete LBBB, as shown in Fig. 6, there is some variation between different hearts in the site of earliest activity of both

Purkinje fibers and muscle fibers of the septal surface. However, if the activation time for each type of fiber is divided into early, intermediate and late periods, as was done for the normal septum, the overall pattern of activation of a single heart is not greatly changed (Fig. 8). Also, as in the normal septum, there is reasonable correspondence between the sequence of activation of the subendocardial Purkinje fibers and that of the muscle fibers of the septal surface after LBBB (Fig. 8). If the time of appearance of the P complexes and M complexes at each location on the septum is related to the ECG (Fig. 9), it is seen that records obtained at all points fall during the latter part of the R wave of Lead II. Also, activation of muscle fibers of the septal surface appears to be complete before the terminal deflections of the ECG.

Discussion

In previous publications,[1-3] bipolar electrograms from different parts of the specialized conducting system of the canine heart have been related to the electrocardiogram. However, the tracings in Figs. 2 and 3 show for the first time bipolar electrograms from all the major subdivisions of the specialized ventricular conducting system (bundle of His, right and left bundle branches, false tendons, right and left Purkinje-papillary junctions and free-running Purkinje fibers) recorded simultaneously from the same heart in situ. Electrograms from peripheral Purkinje fibers are shown in Figs. 4 and 5. We have attempted to employ a uniform terminology to identify the electrograms recorded from each part of the specialized conducting system. This terminology differs in limited extent from that employed previously by this laboratory. The main advantage of the system of nomenclature presented in this study is that the letters used are simple abbreviations of the commonly used anatomic designations of the structures under consideration.

The primary objective of this study was to determine conclusively whether activation of muscle fibers of the left septal surface after LBBB results from the spread of depolarization in the subendocardial Purkinje network. A secondary objective was to determine the sequence of activation of Purkinje fibers and muscle fibers over the entire left septal surface before and after LBBB. We think that valid and meaningful results have been obtained because clear records of the activity of both Purkinje fibers and muscle fibers have been obtained from a large number of points which encompass the entire left septal surface. In addition, it has been possible to record both P and M complexes from many of the same points before and after LBBB. These studies were carried out with complete control of blood pressure, blood flow and temperature of the heart. Also, the method used to record from the septal surface does not result in the local injury associated with the use of needle or plunge electrodes. The reproducibility of the results obtained with this technique has been demonstrated in previous studies.[4,5]

Both before and after LBBB the earliest activity recorded from the left septal surface results from depolarization of Purkinje fibers. Also, both before and after LBBB, Purkinje-fiber activity precedes the activity in adjacent muscle fibers at every site on the septal surface where both P and M complexes are recorded. Unless one postulates a universal failure of conduction from Purkinje tissue to muscle, one must conclude that activity of muscle fibers of the septal surface is the direct result of excitation spreading to these fibers from the subendocardial Purkinje network both before and after LBBB. If, as has been postulated, activation of the muscle fibers of the left septal surface after LBBB resulted from the spread of activity across the septum from the opposite side, it would seem reasonable to conclude that at some locations the M complex would precede the P complex. A possible exception to this statement would arise if the delay in the activation of the left septal surface were due to slow muscle conduction between the deep terminal Purkinje fibers of the right bundle branch system and those of the left bundle branch system in the middle of the septum. In this case the deep branches on the left side would be activated first, then the superficial branches, and then the muscle fibers, as was actually observed. This was not the case. In many hearts, early activity was recorded in the Purkinje system at widely separated points on the sep-

turn This contrasts with the *normal* sequence of activation of the subendocardial Purkinje system and because of the high conduction velocity in these fibers, would necessarily decrease the time required for complete activation After LBBB the time required for complete activation of the septal surface is considerably *less* than the control value This finding is consistent with the concept that after LBBB activity enters the homolateral subendocardial Purkinje fibers at multiple points more or less simultaneously and then spreads to the adjacent muscle fibers at the surface

The results obtained concerning the sequence of activation of the muscle fibers of the left septal surface are similar to those reported previously [4,16,17] In this study and in a previous study in this laboratory [4] the earliest activity was recorded from septal muscle within the area bounded by lines 12 and 14 and lines F and K on the standard grid diagram shown in Fig 1 The apical areas of the septal surface were activated te soon after the earliest point whereas vation of the basal regions uniformly latest. In this study it also has been ssible to show that the over-all sequence of activation of the subendocardial Purkinje network was similar to that of the muscle fibers (Figs. 6 and 8) After LBBB *the sequence of activation of the muscle* fibers of the septal surface is altered because the Purkinje system is activated at multiple points within a short interval of time.

In previous studies there has been some disagreement concerning the site and cause of delay in activation of the left septal surface after LBBB [1,4,17] The two major possibilities considered have been (1) uniformly slow conduction throughout the septum and (2) localized delay at some point between the right and left septal surfaces. The results of the present study of the entire septal surface show that there is considerable delay in the earliest activation of both Purkinje fibers and muscle fibers of the septal surface after LBBB The late activation of the homolateral Purkinje fibers makes unlikely any *direct communication* between these fibers and the Purkinje system of the right septal surface. Also the reduced time required for activation of the homolateral muscle fibers by *the subendocardial Purkinje system* and the short interval between the P and M complexes after LBBB suggest that there is no significant delay between Purkinje fibers and muscle. Moreover after LBBB the earliest activity in the subendocardial *Purkinje fibers of the left septal surface* often was recorded at several points in the periphery of the septum It has been shown[4] that the first depolarization of muscle fibers on the right septal surface is superior and anterior to the anterior papillary muscle. If activation of the left surface after LBBB resulted from direct spread through septal muscle fibers from the earliest point on the right side one would expect to record consistently the first P and M complexes on the left surface only between lines 12 and 14 and J and L on the grid diagram of the left septal surface. This has not been the case. These findings suggest that the site and mechanism of delay as well as the paths of activation of the left septal surface after LBBB require more investigation

Summary

Through utilization of a technique developed in this laboratory it has been possible to study the sequence of activation of the Purkinje fibers and muscle fibers *beneath the endocardium* of the left interventricular septal surface at the same 21 specific points before and after left bundle branch block (LBBB) It has been demonstrated that activation of the Purkinje system (P) at a specific point on the septum precedes that of the adjacent muscle fibers both before and after LBBB It is concluded therefore, that activation of the muscle fibers of the left septal surface is a direct result of excitation spreading to these fibers from the subendocardial Purkinje network both before and after LBBB After LBBB the time required for complete activation of the left septal surface is considerably less than the control value this finding is consistent with the concept that, after LBBB activity spreads within the homolateral subendocardial Purkinje *system* which has been activated simultaneously at multiple points and then spreads to the adjacent muscle fibers of the left septal surface

Representative recordings from all points

on the specialized conducting system (SCS) have been presented including bipolar electrograms from the bundle of His (BH) right bundle branch (RBB) right Purkinje-papillary junction (RPPJ) free-running Purkinje fibers which extend from the base of the right anterior papillary muscle to the endocardium of the wall of the right ventricle (FRP) left bundle branch (LBB) anterior false tendon of the left ventricle (AFT) left anterior Purkinje-papillary junction (LAPPJ) and peripheral Purkinje fibers of the left septal surface at multiple sites (P) In order to facilitate the orderly presentation of data, a system of nomenclature based on the abbreviation for each of the anatomic points from which electrical potentials are recorded has been suggested for use in studying the specialized conducting system (SCS) of the heart.

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REFERENCES

1. Sodi-Pallares, D and Calder R. M New bases of electrocardiography St. Louis, 1956, The C. V Mosby Company
2. Erickson, R. V Scher A M, and Becker R. A. Ventricular excitation in experimental bundle branch block, Circulation Res. 5:5 1957
3. Hoffman, B F and Cranefield, P F Electrophysiology of the heart, New York, 1960 McGraw Hill Book Company Inc.
4. Burchell, H. B Essex, H S and Pruitt, R D Studies on the spread of excitation through the ventricular myocardium II The ventricular septum, Circulation 6 161 1952
5. Medrano, G. A., Sodi-Pallares, D de Micheli A., Bisteni, A Polansky B and Hertault, J A study of the potentials of the Purkinje tissue, AM. HEART J 60:562, 1960.
6. Amer N S., Stuckey J H Hoffman B F Cappelletti, R. R., and Domingo, R. T Activation of the interventricular septal myocardium studied during cardiopulmonary bypass, AM. HEART J 59:224 1959
7. Hoffman, B F., Cranefield P F Stuckey J H Amer N S., Cappelletti, R. R and Domingo, R. T Direct measurement of conduction velocity in the in situ specialized conducting system of the mammalian heart, Proc Soc. Exper Biol & Med 102:55 1959
8. Hoffman, B F., Cranefield, P F Stuckey J H., and Bagdonas, A. A. Electrical activity during the P R interval Circulation Res. 8 1200 1960.
9. Hoffman, B F Cranefield, P F., and Stuckey J H Concealed conduction, Circulation Res 9:194 1961
10. Hoffman B F Kao, C. Y., and Suckling E. E. Refractoriness in cardiac muscle Am J Physiol. 190:473, 1957
11. Lepeschkin, E. Electrophysiology of the heart edited by H Hecht, Ann. New York Acad Sc 65:823 1957
12. Stuckey J H Hoffman, B F., Bagdonas, A. A., and Venerose R. S Direct recordings from chronically implanted electrodes on the specialized conducting system of the heart, Proc. Soc Exper Biol. & Med. 106:00 1961
13. Bagdonas, A. A., Stuckey J H Piera, J., Amer N S., and Hoffman, B F Effects of ischemia and hypoxia on the specialized conducting system of the canine heart, AM. HEART J 61:206, 1961
14. Stuckey J H Hoffman, B F Saksena, C. P Kottmeier P K., and Fishbone, H. Electrode identification of the conduction system during open heart surgery Surg Forum 9:202, 1959
15. Lewis, T The mechanism and graphic registration of the heart beat, London, 1925 Shaw and Sons
16. Lewis, T and Rothschild, M A The excitatory process the dog s heart. II The ventricles, Phil. T Roy Soc (B) 206 181 1915
17. Scher A M Young A. C Malmgren, A. L., and Erickson, R. V Activation of the interventricular septum, Circulation Res. 3:56 1955
18. Pruitt, R. D., and Essex, H E. Potential changes attending the excitation process in the atrioventricular conducting system of bovine and canine hearts, Circulation Res. 8 149 1960.

The local effect of glyceryl trinitrate, nitrite, papaverine, and atropine upon coronary vascular resistance

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The literature is abundant with studies concerned with the effects of various vasoactive substances on the coronary vas- bed.[1-6] None, however, permit a com by weight and molarity of the local -state effects of the active principle glyceryl trinitrate, sodium nitrite, papaverine hydrochloride, and atropine sulfate. In addition, the factor of tonicity and its effects on vascular resistance were not seriously considered.

Therefore, the present study was designed to quantitate the local vascular effects of the active principle of glyceryl trinitrate, sodium nitrite, papaverine hydrochloride, and atropine sulfate on the coronary vasculature. This was done by measuring coronary perfusion pressure at constant coronary blood flow during intracoronary infusion of isotonic solutions of these agents at rates which provided therapeutic blood concentrations.

Materials and methods

The study included a total of 18 mongrel dogs anesthetized with sodium pentobarbital (35 mg. per kilogram) and anticoagulated with heparin (5 mg. per kilogram). The preparation has been described in detail in an earlier communication.[7] The heart was exposed through the right fourth intercostal space. A rotating disc blood oxygenator, blood heat exchanger, and blood pump were interposed between the left femoral artery and plastic cannulae which were inserted into the superior and inferior venae cavae via the right atrium. The body was thus perfused with oxygenated blood at an average rate of 95 ml. per kilogram per minute, and body temperature was maintained at 37° C.

A second pump, interposed between the right femoral artery and the ascending aorta, perfused the coronary vascular bed. By cross-clamping the aorta and pulmonary artery 3 cm. from the heart, the output of this pump was thus diverted through the entire coronary circulation. Flow rate was held constant at an average value of 92 ml. per minute (50 to 125 ml. per minute). Coronary venous blood was collected from the right side of the heart with a cannula threaded through the tricuspid valve in such a way as to render the valve incompetent. Thus blood was returned to the venous limb of the perfusion circuit. Blood from the left side of the heart (from arterioluminal Thebesian and bronchial vessels) was collected with another cannula inserted into the left atrium and ventricle through a superior pulmonary vein. A resistance-wire pressure transducer

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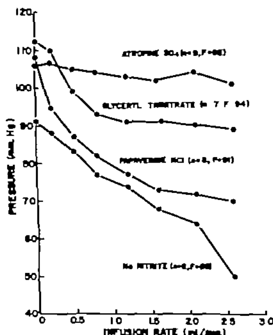


Fig 1 Coronary perfusion pressure as a function of infusion rate of active principle. F Average blood flow in milliliters per minute n, number of dogs.

was utilized to measure pressure in the coronary perfusion tubing just prior to entrance into the ascending aorta.

Isotonic solutions as determined by the Fiske osmometer of glyceryl trinitrate, sodium nitrite, papaverine hydrochloride and atropine sulfate were infused into the coronary perfusion circuit at rates of 0.2 0.5 0.8 1.2 1.6 2.1 and 2.6 ml per minute in that order (Table I) Each rate was maintained for 30 seconds. Coronary perfusion pressure and electrocardiogram were recorded continuously Pressure heart rate and Q-T interval were obtained at the end of each 30-second period at which time the pressures were stable. Since the rate of blood flow through the coronary vascular bed was held constant and pressure in the right heart remained atmospheric changes in resistance were therefore directly proportional to changes in coronary artery pressure The proportion of time spent by the ventricles in systole was calculated from the formula shown below

Results

Dose response effects Coronary vascular pressure decreased as a function of the infusion rate of solutions of glyceryl trinitrate sodium nitrite and papaverine hydrochloride in each animal (Fig 1) Infusion of atropine sulfate failed to produce a regular change in pressure.

At the maximal infusion rate of 2.6 ml per minute glyceryl trinitrate decreased average coronary perfusion pressure by 21.2 per cent whereas sodium nitrite papaverine hydrochloride, and atropine sulfate reduced resistance by 34.0 35.1 and 4.7 per cent respectively (Table II)

Table II presents the change in pressure as a function of the amount of active principle infused per minute It may be seen that on a weight basis, glyceryl trinitrate is by far the most active agent. Table III presents the number of milligrams and moles of each active principle per minute necessary to reduce coronary perfusion pressure by 12 and 20 per cent. From this comparison the active principle of these agents may be ranked according to their potency—in the order glyceryl trinitrate papaverine and nitrite.

Electrocardiographic effects The effects of these substances on the heart rate and Q-T interval allow inferences to be made concerning coronary vessel transmural pressures.[5] Table IV compares perfusion pressure, heart rate Q-T interval and the proportion of time spent by the ventricles in systole during the control period and during the slowest and most rapid rates of infusion Glyceryl trinitrate, nitrite and papaverine failed to change significantly the proportion of a minute spent in systole. Atropine at the maximal infusion rate increased the heart rate Q-T interval and the proportion of time spent by the ventricles in systole by 22 3 and 21 per cent respectively

Discussion

These studies indicate that, in this preparation, isotonic solutions of glyceryl trinitrate sodium nitrite and papaverine

$$\text{Per cent of a minute spent in systole} = \frac{\text{Q-T Interval} \times \text{HR}}{60} \times 100.$$

Table I. Osmolarity and concentration of solutions infused into the coronary vascular bed of the dog

Solution	Osmolarity (mOsm./Kg.)	Concentration (mg./ml.)	Concentration of active principle (mg./ml.)
Glyceryl trinitrate	305	0.10	0.10
Sodium nitrite	315	10.87	7.25
Atropine sulfate	312	2.00	1.70
Papaverine hydrochloride	276	3.25	1.47

Table II. Reduction in coronary perfusion pressure as a function of infusion rate of active principle

Glyceryl trinitrate		Nitrite		Papaverine		Atropine	
Infusion rate (mg./min.)	Pressure change (% of control)	Infusion rate (mg./min.)	Pressure change (% of control)	Infusion rate (mg./min.)	Pressure change (% of control)	Infusion rate (mg./min.)	Pressure change (% of control)
0.02	−2.6	1.45	−3.2	0.29	−12.0	0.34	+0.9
0.05	−12.3	3.63	−8.7	0.74	−19.4	0.85	−0.9
0.08	−17.6	5.80	−15.5	1.18	−24.0	1.36	−1.8
0.12	−19.4	8.70	−18.6	1.76	−28.7	2.04	−2.8
0.16	−19.4	11.60	−25.2	2.35	−32.4	2.72	−3.7
0.21	−20.3	15.23	−29.6	3.09	−33.3	3.57	−1.8
0.26	−21.2	18.85	−34.0	3.82	−35.1	4.42	−2.9

Table III. Comparison of amounts of active principle by weight and molarity necessary to produce equal reduction in coronary perfusion pressure

Agent	12 per cent reduction		20 per cent reduction	
	mg./min.	moles/min.	mg./min.	moles/min.
Glyceryl trinitrate	0.05	2.2×10^{-7}	0.12	5.3×10^{-7}
Nitrite	4.89	1.2×10^{-4}	9.35	2.0×10^{-4}
Papaverine	0.29	8.6×10	0.76	2.2×10^{-6}

hydrochloride produced a decrease in coronary vascular resistance as a function of the rate of steady-state infusion of the active principle. Atropine sulfate produced no apparent change in the vascular resistance.

Although the formulation of an exact potency ratio between various drugs from dose-response curves is difficult, it is possible to arrive at a general approximation of their respective relationships. From the data in Tables II and III, on a weight basis, glyceryl trinitrate is 98 times as potent as the nitrite anion when coronary vascular resistance is reduced by 12 per cent and 88 times as potent when resistance is decreased by 20 per cent. On a molar basis, however, glyceryl trinitrate is 545 and 377 times as potent when resistance is reduced by 12 and 20 per cent, respectively.

Glyceryl trinitrate is 6 times as active as papaverine on a weight basis at both the

12 and 20 per cent reduction levels. When a molar comparison is made glyceryl trinitrate is 4 times as potent as papaverine whether the resistance is decreased by 12 or 20 per cent.

Therefore, at two different infusion levels, at which significant decrease in coronary vascular resistance is produced there is essentially no difference in the relationships of potency of these drugs. Hence on a comparison of weight glyceryl trinitrate is approximately 90 times as potent as nitrite and 6 times as active as papaverine. When this comparison is expressed on a molecular basis, however the organic glyceryl trinitrate is approximately 450 times as potent as the inorganic nitrite anion and 4 times the strength of papaverine. This relationship is also apparent from the curves in Fig. 1.

The fall in coronary vascular resistance most likely resulted from an increase in the caliber of the vessels. Resistance to blood flow through a vascular bed is determined by blood viscosity and vessel geometry.[9] Blood viscosity did not change significantly during administration of these agents because the maximal infusion rate of the solutions diluted the blood by only 2.6 per cent. Furthermore, changes in viscosity due to reorientation of the red blood cells in the flowing stream need not be seriously considered since flow rate was held constant and pressures and flows were well above the range in which this phenomenon occurs.[10]

Because intramyocardial pressure was not measured it cannot be stated with certainty whether the dilation was active due to a change in the contractile state of the smooth muscle within the vessel wall or passive due to an increase in vessel transmural pressure subsequent to a decrease in intramyocardial pressure. The absence of a change in the per cent of a minute spent in electrical systole suggests that intramyocardial pressure was not altered by changes in the relationship of mechanical systole to diastole but does not provide information regarding the strength of myocardial contraction. Passive dilation due to dehydration of the vessel wall need not be considered because all solutions infused were isosmotic to plasma.

Thus, glyceryl trinitrate nitrite and papaverine produce coronary vascular dilation when administered locally over the concentration ranges which might occur during therapy. The fact that atropine increased the proportion of a minute spent in systole without significantly changing perfusion pressure, suggests that atropine also dilates coronary vessels.

Previous studies[11] have shown that the sodium ion produces no change in coronary vascular resistance. Hence, the dilation

Table IV. Effect of active principles upon several parameters at minimal and maximal rates of infusion

Agent	Infusion rate (ml./min.)	Coronary pressure (mm. Hg)	Heart rate (beats/min.)	Q-T interval (sec.)	Time in systole (%)
Control	0	113	128	27	51
Glyceryl trinitrate	0.2	110	127	27	51
Glyceryl trinitrate	0.6	89	120	28	53
Control	0	92	116	31	41
Nitrit	0.2	88	116	31	42
Nitrit	0.6	60	113	32	42
Control	0	108	134	31	66
Papaverine	0.2	95	134	31	65
Papaverine	0.6	70	130	35	69
Control	0	103	116	28	56
Atropine	0.2	107	117	28	56
Atropine	0.6	100	142	29	68

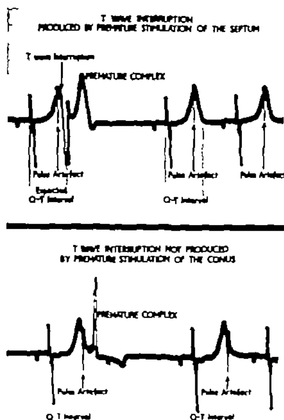


Fig 1 The effect of the site of stimulation on the production of the S-by V type of interruption. In the upper trace a premature ventricular complex elicited from the septum is seen to be propagated well within the expected Q-T interval as measured from the subsequent complex On the latter complex a slightly more premature stimulus has not been effective In the lower trace the last effective stimulus on the conus has failed to produce a complex which is sufficiently premature to interrupt the T wave.

consisted of an isolated differential input stage and five successive push pull stages. The amplified ECG was recorded photographically from a blue short-persistence cathode-ray tube and could be followed on a long persistence cathode-ray tube with a slow time base

Hearts were stimulated electrically with square-wave pulses of 2 5 ma. strength and 1 msec. duration. This stimulating pulse was about ten times the average strength of stimulus required to produce a propagated response during diastole. Premature stimuli were triggered after a delay by either the main deflection of the preceding QRS complex or by a pacemaking impulse

In order to study propagation during the inscription of the T wave premature complexes were first elicited beyond the T wave of the preceding complexes and then the delay between the premature and the preceding complexes was shortened to produce if possible progressive encroachment on the preceding T waves.

Results

1 Production of S-by V type of interruption.

A EFFECT OF DIFFERING SITES OF STIMULATION It was sometimes possible to interrupt the T waves of spontaneous supraventricular complexes by premature ventricular complexes produced by stimulation of the ventricular septum (Fig 1) If the pulmonary conus was used as a site to elicit such premature ventricular complexes interruption of the T wave was never produced

Serial premature complexes elicited after the T wave were of uniform shape but complexes elicited either at the termination or during the inscription of the T wave were usually of multiform shape (Table I) despite their origin from a single focus.

Furthermore, it was found that stimuli of varying strengths applied to the pulmonary conus became ineffective much sooner in relationship to the T wave than did comparable stimuli applied to the ventricular septum Strong stimuli applied to the septum remained effective even on the ascent of the T wave.

B EFFECT OF AN ELECTROLYTE SOLUTION DESIGNED TO PROLONG CONDUCTION TIME. When hearts were perfused with a solution which contained half the usual concentration of potassium (2 5 mEq per liter) and twice the usual content of calcium (10 mEq per liter) stimulation of the ventricular septum produced very marked interruption of the T wave of the S-by V type in all experiments. Under such conditions, only a minimal degree of interruption of the T wave was seen when the pulmonary conus was stimulated

Table I sets out the frequency with which interruption of the T wave occurred when the septum and the pulmonary conus were stimulated in experiments involving 12 hearts which were perfused first with normal Krebs-Henseleit solution and then with the modified solution

Polymorphism of ventricular complexes

elicited during the inscription of the T wave was commonly seen. To ensure that such polymorphism was not due to a change in the point of contact made by the stimulating electrodes, the delay before application of the electrical stimulus was increased again after maximum interruption of the T wave had been recorded. A reversion of the ectopic complexes to their former uniform shape invariably occurred.

Ventricular fibrillation was most commonly precipitated in those experiments which favored maximum interruption of the T waves, i.e. stimulation of the ventricular septum while the heart was being perfused with a hypokalemic solution.

C. EFFECT OF MYOCARDIAL ISCHEMIA. When an area on the anterior aspect of the left ventricle was prematurely stimulated, T waves of the preceding spontaneous supraventricular complexes were sometimes interrupted to a minimal extent (5 of 12 experiments). After the same area had been made ischemic by ligation of the anterior descending branch of the left coronary artery, T-wave interruption of considerable degree was produced by premature stimulation of the same point in 10 of 11 experiments (Fig. 2). In 3 of these experiments, ventricular fibrillation was a sequel of interruption of the T wave. Premature stimulation of the ventricle outside the ischemic area did not produce S-by-V type of interruption.

2. *Attempted production of S-by-S type of interruption.* S-by-S type of interruption was not produced when an attempt was made to interrupt the ventricular complexes of spontaneous supraventricular beats by premature ventricular complexes of supraventricular origin. Any attempt to make the auricular stimulus more premature once the ventricular component had reached the termination of the preceding T wave merely resulted in a prolongation of the P-R interval until A-V block of the premature supraventricular complex occurred. Adrenaline did not facilitate A-V conduction sufficiently to allow interruption of the T wave.

3. *Production of V-by-V type of interruption.* The V-by-V type of interruption could always be produced by delivering a burst of suitably spaced stimuli to any point on the ventricles (Fig. 3). Furthermore, it was possible to interrupt the T waves of ventricular complexes produced by a ventricular pacemaker with premature complexes elicited from any nearby point in 9 of 10 experiments. However, in only 1 of 10 experiments was it possible to produce such interruptions if the premature interrupting complexes were elicited from a point more or less diametrically opposite the pacemaking electrodes, there being no change in the frequency of stimulation.

Polymorphism of premature ventricular complexes elicited during the inscription of the preceding T waves occurred even though these were elicited from the same focus. Ventricular fibrillation occurred in 3 of these experiments.

4. *Attempted production of V-by-S type of interruption.* The V-by-S type of interruption was not produced. The reason for this was probably that retrograde depolarization of nodal tissue prevented the early conduction of premature supraventricular complexes to the ventricles.

5. *Ventricular fibrillation and T-wave interruption.* In the preceding experiments ventricular fibrillation not infrequently

Table I

Perfusing fluid	Site of stimulation	Number of experiments	T-wave encroachment	Polymorphism on or at the termination of the T wave	Ventricular fibrillation
Normal Krebs-Henseleit	Pulmonary conus	12	0	5 (Minimal)	0
	Ventricular septum	12	4	10	0
Modified Krebs-Henseleit	Pulmonary conus	12	3 (Minimal)	10 (Minimal)	1
	Ventricular septum	12	12	12	3

*The results of 12 experiments in which attempts were made to interrupt the T waves of spontaneous supraventricular beats by stimulating the pulmonary conus and ventricular septum during perfusion with normal Krebs-Henseleit solution and similar solution modified by reduction in K⁺ and an increase in the calcium content.

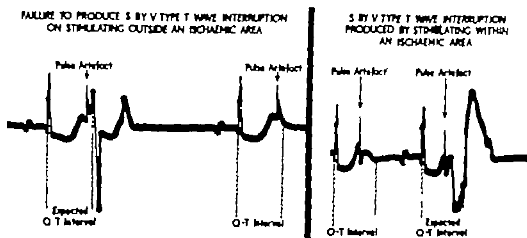


Fig. 2. The effect of localized ventricular ischemia on the production of the S-by-V type of interruption. In the trace on the left, interruption of the T wave has not been produced by placing the premature stimulus outside the ischemic area, but in the trace on the right, with the premature stimulus placed within the ischemic area, marked interruption of the T wave has been produced. (In these examples there has been some vertical displacement of the trace by the stimulus.)

followed T wave interruption produced by electrical stimulation on the T wave (Fig. 4). The strength of the stimulus used was never more than ten times threshold. Furthermore, on only one occasion was fibrillation precipitated under circumstances not conducive to interruption of the T wave.

When hearts were perfused with a solution which had a low content of potassium and the ventricular septum was stimulated prematurely in relationship to preceding supraventricular complexes, 3 of 12 hearts fibrillated. Stimulation of the pulmonary conus under similar circumstances produced fibrillation of one heart.

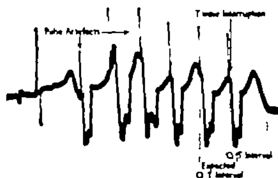


Fig. 3. Series of V-by-V type of T-wave interruptions showing multiform type produced by delivering a burst of suitably spaced stimuli to the ventricles. The degree of interruption of the T wave may be judged from the Q-T interval of the last complete complex.

Fibrillation was not precipitated by stimulation of the anterior surface of the ventricle before ligation of the ramus descendens; however, after this area had been made ischemic, fibrillation occurred in 3 of 11 experiments.

During the production of the V-by-V type of interruption, ventricular fibrillation occurred in 3 of 11 experiments. Ventricular fibrillation was not precipitated in unsuccessful attempts to produce T wave interruption even though stimuli were falling during the inscription of the T wave.

Discussion

In these experiments, interruption of the T wave was produced by premature stimulation of areas of the ventricles which had either by virtue of their situation or state repolarized before other areas.

T wave interruption of the S-by-V type was produced when the ventricular septum was prematurely stimulated after the passage of a supraventricular impulse but not by the premature stimulation of the pulmonary conus.

Such interruptions were exaggerated when the intracardiac conduction time was prolonged by perfusing the heart with Krebs-Henseleit solution which contained half the usual concentration of potassium and twice the usual concentration of calcium. The latter alteration was necessary to decrease cardiac excitability[4] and reduce

the frequency with which ventricular fibrillation was found to follow interruption of the T wave in the presence of a lowered potassium.

S-by-V type of T wave interruption was also produced by stimulating an ischemic area of ventricular myocardium. It has been shown that ischemia shortens the local monophasic action potential.[4] Thus such an ischemic area repolarizes before the surrounding normal muscle and premature stimulation will result in propagation from such an area while the surrounding parts are still contributing to the T wave.

Further confirmation that a spatial mechanism underlies the R-on-T phenomenon was obtained from experiments designed to reproduce the V-by-V type of interruption. If the premature interrupting complex was elicited from the same area as the preceding complex, interruption of the T wave could be produced quite regularly. Attempts to interrupt this same complex from a point judged to be diametrically opposite its site of origin failed in all but one experiment.

A "spatial" mechanism refers to T wave interruption being due to propagation of a premature stimulus through an area of repolarized myocardium while recovery and contribution to the T wave is still being made by other areas. This may be contrasted with a "temporal" mechanism—the subject of a later paper—wherein the interruption may be due in part at least to propagation of a premature stimulus before complete local repolarization has occurred.

It should be noted that the phenomenon of T wave interruption in no way conflicts with the findings of Moe and associates[9] that stimulation during the T wave resulted in a propagated response which began not on but immediately after the completion of the T wave. These authors used contiguous punctate bipolar electrodes which do not record the asynchronism of repolarization that occurs between more widely separated myocardial areas.

Mention must be made of the failure to produce either the S-by-S or V-by-S forms of interruption even though both forms have been observed clinically.[4] Failure was related to the premature supraventricular complex not being conducted through the atrioventricular tissues in time to interrupt the preceding complex. This probably reflected an observation that the duration of transmembrane potentials recorded from Purkinje fibers was considerably longer than that of those of plain ventricular muscle.[10] Since this experimental work was completed a drug referred to as U-0882 has been described which has properties similar to amarine. Although U-0882 prolongs the refractory period of the atrial and ventricular myocardium it apparently does not prolong appreciably the conduc-

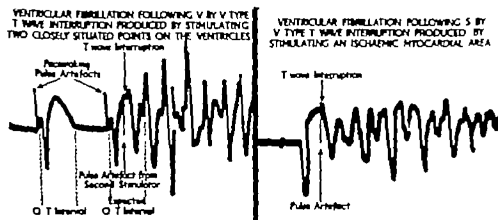


Fig. 4. The trace on the left shows chaotic rhythm after a V-by-V type of interruption precipitated by premature stimulation of the ventricles adjacent to the pacemaking electrodes. The trace on the right shows a similar arrhythmia by V type of interruption precipitated by stimulation of an ischemic ventricular area.

tion time from atria to ventricles.[9] This compound sensitizes the heart to ventricular fibrillation and could well provide the necessary circumstances for the successful experimental production of these S-by-S and V-by-S forms allowing premature excitation of the ventricles from the atria while the more peripheral parts of the ventricles are still recovering from the previous impulse.

In this series of experiments ventricular fibrillation was never precipitated when stimulation was made after the T wave. Nor was fibrillation produced if stimulation made during the inscription of the T wave (with one exception) did not produce interruption of the T wave. However, when stimulation was made on the T wave under circumstances which produced interruption of the T wave, ventricular fibrillation was not infrequently precipitated. It has long been known that stimulation of the ventricular myocardium during the inscription of the T wave may produce ven icular fibrillation,[7,8] but the required gth of current was several hundred es threshold, whereas the strength of current used in the present experiments was only ten times threshold. The discrepancy lies in the site used for stimulation. In the work quoted above, areas on the anterior aspect of the ventricles were used—areas which, if stimulated prematurely in relation to a supraventricular impulse, would not readily allow interruption of the T wave.

The likely mechanism underlying the precipitation of ventricular fibrillation in the present series of experiments came from further consideration of the form of the premature complexes elicited under varying circumstances. Premature ventricular complexes elicited beyond the T wave during diastole were always of a uniform appearance. In contrast, complexes obtained by stimulation of the same site during the inscription or termination of the T wave were frequently of multiform appearance and differed both from each other and from the form of complex seen beyond the T wave. Thus the propagation front of a very premature systole may meet tissue which has not fully recovered from the passage of the previous impulse. Such refractory areas may be bypassed (with resultant multiformity of such complexes) and the stage be set for re-entry and the precipitation of a chaotic rhythm.

The relationship between T wave interruption and the precipitation of ventricular fibrillation is not incompatible with the ectopic focus theory advanced by Prinzmetal,[11] who looked upon fibrillation as being the result of a breakdown in organized activity secondary to discharges arising with such a frequency from an ectopic focus that the myocardium cannot respond in an orderly manner. It does not seem necessary to postulate that such an ectopic focus need always continue to fire once activity has become disorganized, because re-entry may easily be envisaged as perpetuating the fibrillatory process. A propagated impulse which arises very prematurely in relationship to the repolarization process elsewhere in the myocardium replaces par excellence such a multitude of discharges. In other words, one of the many impulses which originate from a focus may well precipitate fibrillation by producing the conditions which are associated with a V by V type of interruption, but only this one impulse can be considered essential to the initiation of the fibrillatory process.

A parallel may be drawn between the production of T wave interruption and ventricular fibrillation by the stimulation of an ischemic myocardial area and the clinical association of myocardial infarction, T wave interruption, and sudden death.[4] An ectopic focus established within an ischemic area may fire prematurely and, because of the shortened repolarization time within the area, a propagated response may interrupt the T wave of the preceding complex.

Summary

The mechanism of interruption of the T wave has been described. It has been shown that interruption may be produced if an area of repolarized myocardium is stimulated before other areas have recovered from the passage of the preceding impulse. However, the extent of interruption of the T wave may be increased by propagation of the premature impulse before local repolarization has been completed.

Interruption of the T wave was produced under the following conditions (1) by the premature stimulation of the ventricular septum after the passage of a supraventricular impulse (2) by the premature stimulation of the site of origin of an ectopic ventricular complex and (3) by the premature stimulation of an ischemic area of ventricular myocardium after the passage of a supraventricular complex.

Ventricular fibrillation was frequently observed to be precipitated by interruption of the T wave and evidence has been produced which suggests that such very premature impulses may meet refractory tissue which is bypassed. Re-entry into such bypassed areas might well explain the onset of ventricular fibrillation.

I think that these experimental results have provided a physiologic basis for the R-on-T phenomenon as encountered clinically and have confirmed the relationship of T wave interruption to serious ventricular arrhythmias.

I gratefully acknowledge the suggestion by Sir Horace Smirk that I make the R-on T phenomenon a subject for experimental investigation, and the long hours of work spent by Mr. A. T. Wallis in the planning and construction of the electronic apparatus.

REFERENCES

1 Fastier F N and Smirk, F H Some properties of amarine, with special reference to its use in conjunction with adrenaline for the production of idioventricular rhythms, J Physiol. 107:318, 1948.

2. Fastier F N Electrocardiographic features of adrenaline syncope, J Physiol. 112:359 1951

3 Smirk, F H R waves interrupting T waves, Brit. Heart J 11:23 1949

4 Smirk F H., and Palmer D G A myocardial syndrome. With particular reference to the occurrence of sudden death and of premature systoles interrupting antecedent T waves, Am. J Cardiol. 6:620, 1960.

5 Hoffman, B J., and Suckling, E. E. Effect of several cations on transmembrane potential of cardiac muscle, Am. J Physiol. 186:317 1956.

6. Wiggers, H C., and Wiggers, C. J The interpretation of monophasic action potentials from the mammalian ventricle indicated by changes following coronary occlusion Am. J Physiol. 113:683, 1935

7 Wiggers, C. J and Wegria, R. Ventricular fibrillation due to single, localized induction and condenser shocks applied during the vulnerable phase of ventricular systole, Am J Physiol. 128:500, 1940.

8. Moe, G K., Harris, A. S., and Wiggers, C J Analysis of the initiation of fibrillation by electrocardiographic studies, Am. J Physiol. 134:473 1942.

9 Moore, J L., and Swain, H. H. Sensitization to ventricular fibrillation. I Sensitization by a substituted propiophenone U-0882, J Pharmacol. & Exper Therap. 128:8289 1960.

10. Trautwein, W Gottstein, U and Dudel, J Der Aktionsstrom der Myokardfaser im Sauerstoffmangel, Pflügers Arch. ges. Physiol. 49:260 1954 Quoted by Brooks, C. McC et al. Excitability of the heart, New York, 1955 Grune & Stratton, Inc p. 107

11 Prinzmetal, M Corday E Brill, I. C Oblath R. W and Kruger H. E. The auricular arrhythmias, Springfield, Ill. 1952, Charles C Thomas Publisher

Importance of oxygen differentials in the etiology of ventricular fibrillation after ligation of the coronary artery

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According to Brofman Leighninger and Beck[1] the frequent development of ventricular fibrillation (VF) and death soon after the occlusion of a major coronary artery is dependent on the ectopic impulses ich arise as a result of the current of oxygen differential between the ischemic and well-perfused areas of the ventricular myocardium Beck referred to this process as mechanism death [1] or self-electrocution of the heart [2] and emphasized the importance of well-oxygenated muscle "in juxtaposition to poorly oxygenated myocardium Badeer and Horvath[3] recently presented evidence which failed to support the concept of ischemic nonischemic boundaries and the existence of marked oxygen differentials as the basis for the fibrillation that follows coronary occlusion It was noted that in open-chest dogs complete arrest of the coronary arterial inflow to the entire myocardium caused VF Since current opinion[4,5] still adheres to the view of Beck it was necessary to test the hypothesis further by other methods of experimental approach

It was reasoned that if the concept of oxygen differential" was true increasing the differential by elevating the oxygen tension in the well perfused areas of the myocardium should favor the development of ectopic foci and VF The oxygen differential was increased by the administration of 100 per cent oxygen during coronary occlusion [6,7]

The present study deals with the influence of inhalation of oxygen on the incidence of VF after ligation of the left anterior descending coronary artery in dogs.

Methods

Fifty mongrel dogs of both sexes were anesthetized with intraperitoneal sodium pentobarbital (35 mg per kilogram) Body weights were limited to a range of 8 4 to 15 8 kilograms, since heart size probably influences the susceptibility to VF [8] Blood pressure was recorded with a mercury manometer from the left common carotid artery The chest was entered by a mid sternal incision and artificial respiration at a rate of about 13 per minute was carried out with a Starling pump The stroke volume of the pump ranged between 150 and 200 ml so as to maintain an adequate color of the animal and avoid respiratory effort The phrenic nerves were removed and the lungs were covered with gauze moistened with saline To gain access to the left coronary artery the ribs were separated at an appropriate level on the left side A small incision was made in the pericardium and the left auricular appendage was pulled away with a ligature The anterior descending branch of the left

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coronary artery was dissected about 5 millimeters below its origin so as to avoid the inclusion of the (anterior) septal artery which may arise below the origin of the left circumflex.[9,14] A nylon thread (20-pound test casting line) was passed around the artery at the point of dissection. A control electrocardiogram (Lead II) was recorded before the artery was ligated.

Twenty-five dogs were ventilated with room air throughout the entire experimental period and 25 others were given 100 per cent oxygen when the vessel was ligated.

After the artery was ligated, the electrocardiogram was taken at frequent intervals and blood pressure was recorded continuously for 1 hour. If no VF supervened by the end of this period, the experiments were terminated. Most investigators report that if VF develops, it will occur within 30 minutes after occlusion of this artery.[11,12] In all experiments the artery was dissected post mortem and the location of the septal artery with respect to the ligature was noted. Experiments in which the septal artery was included in the ligature were excluded from this report except two oxygen experiments (Dogs No. 54 and 65) in which fibrillation did not occur despite septal occlusion. The air and oxygen experiments were conducted alternately. Temperature of the room air was recorded.

Results

The experimental data on 25 dogs which were ventilated with air are summarized in Table I. The incidence of ventricular arrhythmias which led to VF within 1 hour of ligation of the coronary artery was 20 per cent. The average postocclusion period before the onset of VF was 7.72 minutes. The incidence of ventricular arrhythmias, in the form of premature beats and tachycardia from which the heart recovered was 56 per cent. The remaining 24 per cent of the dogs did not exhibit any arrhythmias at all during the 1 hour period after ligation.

Table II shows the experimental data from another group of 25 dogs in which the lungs were ventilated with 100 per cent oxygen during occlusion of the coronary artery. The incidence of VF was 28 per cent and the average period before the onset of VF was 11.4 minutes. The incidence of arrhythmias which did not lead to VF within 1 hour of ligation was 48 per cent. There were no arrhythmias in 24 per cent of the dogs.

From these data it is noted that there was no statistically* significant difference in the incidence of arrhythmias and VF in the two groups of dogs. Furthermore, there was no correlation between the development of VF and such parameters as heart rate, blood pressure, sex, or ambient temperature of the air.

The incidence of VF in all the experimental animals was 24 per cent.

Discussion

The incidence of VF in our experiments was more or less in agreement with the observations of the majority of investigators who have ligated the anterior descending coronary artery in anesthetized dogs. The largest series reported was that of Stephenson and associates,[14] who noted VF within 30 minutes in 28 per cent of a total of 330 dogs. They used inhalation of air and ligated the artery at its origin. Van Citters[11] using inhalation of 100 per cent oxygen obtained 33 per cent VF when the artery was ligated distal to the septal artery (12 dogs). Wexler and Patt[1] reported VF in 30 per cent of animals breathing 95 per cent oxygen with 5 per cent carbon dioxide (83 dogs). The exact location of the ligature was not stated. Senderoff and co-workers[15] using inhalation of air obtained VF in 88 per cent of their animals (25 dogs). The artery was ligated exactly at its origin. These variations in the incidence of VF reported in the literature seem to be related mostly to the site of the ligature in relation to the origin of the septal artery and to the total number of experiments performed. Probably the latter is one of the most important factors that is often overlooked.

*The difference in the incidence of VF between the dogs ventilated with air and those ventilated with oxygen (8 per cent) was less than twice the standard error of the difference between the two percentages (2 × 12 per cent). Standard error of the difference between two percentages =

$$\sqrt{\frac{p_1 \times q_1}{n_1} + \frac{p_2 \times q_2}{n_2}}$$

where p = percentage showing response, q = 1 − p, and n = number of observations.

The concept of "current of oxygen differential" as propounded by Brofman and associates[1] stated that ectopic discharges and VF after coronary occlusion were dependent upon the establishment of currents between ischemic and nonischemic areas of ventricular myocardium and that these currents arose as a result of the marked *difference* in the oxygen tension (oxygen differential) between the two regions. This view was supported by the observation that fatal asphyxia or anoxia in the dog did not lead to VF but stopped the heart in asystole.[1,2,16,17] Here the oxygen tension in the ventricular myocardium presumably dropped more or less uniformly so that very weak or no currents were created.

If this concept were true, then total arrest of the entire coronary arterial flow should also cause very weak or no "currents of oxygen differential" and should stop the heart in asystole. But, in fact, it caused ectopic beats which led to VF within a few minutes.[8]

In the present study the assumption was made that inhalation of oxygen increased the "oxygen differential" between the fully ischemic and the perfused regions of the ventricular myocardium. This was based on the investigations of Sayen and associates[6,7] who demonstrated repeatedly that inhalation of 100 per cent oxygen increased the tension of oxygen (polarographic method) by 50 to 200 per cent or more in perfused areas of ventricular myocardium, whereas in areas made ischemic by coronary

Table I. Open-chest dogs ventilated with room air during coronary occlusion

Dog number	Sex	Weight of dog (Kg.)	Heart weight (Gm.)	Room temp. (°C)	Heart rate/min. before occlusion	Mean arterial pressure (mm. Hg): Before occlusion	Mean arterial pressure (mm. Hg): Before terminal event
1	M	10.4	84	—	177	120	120
4	M	13.0	87	—	162	100	80
6	F	15.0	95	—	180	120	130
10	M	10.0	62	30	187	140	135
26	F	11.7	83	23	145	100	90
28	F	11.5	75	23	180	95	85
31	F	10.0	68	21.5	150	105	100
33	F	12.1	75	21	140	125	135
35	F	12.8	87	22	170	115	115
36	F	13.8	93	22	160	115	95
39	M	10.5	88	18	133	108	70
41	F	12.6	93	19	156	80	90
43	M	15.8	91	21	150	110	110
45	M	13.2	87	20	130	80	85
47	M	12.6	80	22	140	90	90
50	F	8.4	51	21.5	207	115	130
53	F	13.1	101	18	140	125	110
55	M	11.4	74	19	160	100	100
57	F	13.0	101	22	135	90	95
59	M	13.0	82	26	170	88	75
61	F	13.3	104	27.5	166	95	75
64	F	10.5	84	27	216	150	120
66	M	14.0	97	29	150	140	140
69	M	15.4	103	28.8	135	105	115
71	M	11.0	84	29.4	210	130	105
Mean		12.5	85				
S.D.		±1.8	±12.8				

PB, Premature beats. T, Tachycardia. VF, Ventricular fibrillation.

occlusion the oxygen tension rose hardly at all. In normally perfused myocardium the maximum values of oxygen tension were attained within 1 minute of inhalation and the changes were reversible. Our observation that the incidence of VF was not different in dogs ventilated with oxygen and in those ventilated with air opposed the concept of "oxygen differentials."

That acute ischemia of heart muscle induced changes in the resting and action potentials of the muscle fibers have been demonstrated.[11-13] The amplitude and duration of the action potential as well as the resting membrane potential were reduced in ischemic muscle.[14] According to Brooks and associates[15] such alterations generated currents between the ischemic and normal muscle and these currents, when sufficiently strong, caused the arrhythmias. The fact that total ischemia of the entire myocardium caused VF does not support such a concept.[3] It is possible that in localized occlusions the currents created by "ischemic injury" are concomitants and not the cause of ectopic activity. The mechanism responsible for ectopic rhythms and VF may reside entirely within the partially or totally ischemic myocardial cells irrespective of the existence of normally perfused myocardium adjacent to it and the existence of "injury currents" of high intensity.

From our present observations and previous study[3] it may be concluded that ectopic discharges and VF after coronary occlusion

Ventricular arrhythmias after occlusion	*Terminal event*
PB and T from 2.5 to 13 min	No VF until end of 1 hr
Occasional PB	No VF until end of 1 hr
PB and T from 2 to 5 and 12 to 22 min	No VF until end of 1 hr
Occasional PB	No VF until end of 1 hr
PB and T from 2 to 11 min	No VF until end of 1 hr
PB from 12 to 39 min.	No VF until end of 1 hr
PB and T from 5.75 to 10 and 17 to 25 min	No VF until end of 1 hr
None	No VF until end of 1 hr
PB from 1.75 to 15 min. T from 16 to 26 min	No VF until end of 1 hr
None	No VF until end of 1 hr
PB and T from 2.25 min. until VF	VF 5.25 min. after occlusion
None	No VF until end of 1 hr
PB from 2 to 6 and 19 to 24 min	No VF until end of 1 hr
None	No VF until end of 1 hr
None	No VF until end of 1 hr
None	No VF until end of 1 hr
PB from 16 to 33 min. T from 2.25 to 12 min	No VF until end of 1 hr
PB and T from 2 to 10 min	No VF until end of 1 hr
PB from 4.75 to 8 and 16 to 22 min.	No VF until end of 1 hr
PB and T from 1.6 min. until VF	VF 13.75 min. after occlusion
PB and T from 2.25 min. until VF	VF 3.17 min. after occlusion
PB and T from 1.75 min. until VF	VF 2.08 min. after occlusion
PB and T from 1.5 to 11 min	VF 14.33 min. after occlusion
Pulsus alternans from 26 to 27 min.	No VF until end of 1 hr
PB from 1.33 to 4 min	No VF until end of 1 hr

are unrelated either to the magnitude of oxygen differentials or to the currents that may exist between the normally perfused and ischemic ventricular myocardium. This does not mean that the origin of ectopic impulses is not related to the lack of oxygen or blood supply to the myocardium (be this localized or generalized).

In 1954 Harris and co-workers[38] postulated that potassium released from ischemic heart muscle diffused and acted as an excitant to the adjacent heart muscle, thus setting up ectopic foci. Recently, Wexler and Patt[14] presented evidence which failed to support the hypothesis that liberation of potassium from ischemic heart muscle was responsible for the VF which may set in soon after coronary occlusion.

Many biochemical studies have been carried out on ischemic or anoxic heart muscle, but at present it is impossible to correlate the observed changes with the development of ectopic rhythms and VF. Much work remains to be done at the cellular level before the mechanism of ectopic discharges soon after coronary occlusion is elucidated.

Arrhythmias after coronary occlusion must be related (directly or indirectly) to one or both of two major disturbances: (1) hypoxia or asphyxia of heart muscle and (2) arrest of the flow of plasma. To our knowledge, no experiments have been designed to dissociate these two primary disturbances. The fact that acute generalized fatal asphyxia or hypoxia in dogs does not induce VF suggests that the VF after coronary occlusion, be it localized or generalized, may be related to the arrest

Table II. Open-chest dogs ventilated with 100 per cent oxygen during coronary occlusion

Dog number	Sex	Weight of dog (Kg.)	Heart weight (Gm.)	Room temp. (°C)	Heart rate, min. before occlusion	Mean arterial pressure (mm. Hg): Before occlusion	Mean arterial pressure (mm. Hg): Before a terminal event
2	M	10 4	56	—	180	90	90
5	M	9 5	56	—	150	85	120
7	F	13 9	85	—	200	125	125
25	M	11 0	80	25	150	90	90
27	F	13 0	100	20 5	130	5	60
29	M	13 2	86	21 3	140	80	80
34	M	11 7	69	21	127	95	60
37	M	15 4	102	21	140	115	110
38	F	12 0	80	19 5	115	105	90
40	M	12 4	63	18	120	110	120
46	M	10 8	60	20	153	80	85
48	M	14 9	66	21	160	100	103
49	M	8 7	45	21	145	85	65
51	M	13 0	91	21 2	163	120	130
52	F	13 8	80	20	145	65	50
54	M	12 0	84	19	153	95	95
56	F	12 2	98	23 2	145	115	110
58	F	12 9	71	22 2	133	80	82
60	F	12 3	96	27	130	103	123
62	F	10 0	87	25 7	206	125	110
63	F	15 0	110	28	185	110	93
65	M	12 0	7	27 5	140	120	130
67	F	11 0	85	28 8	160	145	120
70	F	13 0	84	29	175	125	105
72	M	15 0	10	29	183	100	110
Mean		1 4	81				
S.D.		±1 6	±16 9				

of plasma flow rather than to the lack of oxygen per se. Contrary to most observers Coffman and Gregg[8] have recently reported *electrocardiographic* VF in 33 per cent of asphyxiated closed-chest dogs. In these experiments the electrically recorded VF occurred approximately 15 minutes after the fall of blood pressure to about zero. I have personally noted in exposed dog hearts that such electrocardiographic VF which may occur prior to cessation of all electrical activity is associated with hardly detectable contractions in a *few* muscle fibers of the ventricles. We believe that such VF is not quite comparable to that of coronary occlusion in which the arrhythmia develops relatively early and when the heart is visibly contracting and ejecting blood. Here the ventricles exhibit grossly visible mechanical fibrillation. Beck[12] has also pointed out the dissimilarity between the two situations.

Summary and conclusions

In a series of 25 open-chest dogs ventilated with room air the incidence of ventricular fibrillation (VF) after ligation of the anterior descending coronary artery (excluding the septal artery) was 20 per cent. In another group of 25 dogs a similar ligation led to VF in 28 per cent of the animals when the lungs were ventilated with 100 per cent oxygen during occlusion. This difference was not significant statistically. Sayen and associates[4,7] have demonstrated by the polarographic method that inhalation of 100 per cent oxygen increased the oxygen differential between the ischemic and normally perfused myocardium.

From the foregoing it was concluded

Ventricular arrhythmias after occlusion	Terminal event
None	No VF until end of 1 hr
Occasional PB from 18 to 21 min	No VF until end of 1 hr
PB and T from 1 to 3 min.	VF 9 min. after occlusion
PB and T from 1.83 to 17 min	No VF until end of 1 hr
PB and T from 2.75 min. until VF	VF 10.08 min after occlusion
None	No VF until end of 1 hr
PB from 3 to 5 min T from 15 min	VF 17.5 min after occlusion
None	No VF until end of 1 hr
PB from 27 to 30 and 48 to 50 min	No VF until end of 1 hr
None	No VF until end of 1 hr
None	No VF until end of 1 h
Few PB only	No VF until end of 1 hr
Few PB only	No VF until end of 1 hr
Occasional PB from 27 to 60 min	No VF until end of 1 hr
PB and T from 3 min. until VF	VF 4.17 min after occlusion
PB and T from 3.5 to 10 and 16 to 25 min.	No VF until end of 1 hr
PB and T from 4.3 to 7 min.	No VF until end of 1 hr
Few PB only	No VF until end of 1 hr
None	No VF until end of 1 hr
PB and T from 1.33 min until VF	VF 3.33 min after occlusion
Occasional PB	No VF until end of 1 hr
PB from 2.5 to 4 min	No VF until end of 1 hr
PB and T from 1.23 to 21 min.	No VF until end of 1 hr
PB and T from 1.75 min. until VF	VF 2.08 min after occlusion
PB and T from 15 to 26 and from 29 min until VF	VF 31.66 min after occlusion

that the oxygen differential between ischemic and perfused regions of the ventricular myocardium does not play a role in the development of VF after coronary occlusion. However, this does not rule out the importance of myocardial ischemia in VF.

Some theories in regard to the origin of ectopic discharges after acute coronary occlusion were briefly discussed.

REFERENCES

1. Brofman, B. L., Leighninger, D. S., and Beck, C. S.: Electric instability of the heart. The concept of the current of oxygen differential in coronary artery disease, Circulation 13:161, 1956.
2. Beck, C. S.: Circulatory system: heart surgical operations, in Glasser, O., editor: Medical physics, Chicago, 1960, The Yearbook Publishers, Inc., vol. 3, p. 126.
3. Badeer, H., and Horvath, S. M.: Role of acute myocardial hypoxia and ischemic nonischemic boundaries in ventricular fibrillation, Am. Heart J. 58:706, 1959.
4. Hammond, J. F.: Ventricular fibrillation in hearts too good to die (editorial), J.A.M.A. 170:471, 1959.
5. Crumpton, C. W.: Clinical aspects of coronary heart disease, in Luisada, A. A., editor: Cardiology: an encyclopedia of the cardiovascular system, New York, 1959, McGraw-Hill Book Company, vol. 3, part 10, p. 35.
6. Sayen, J. J., Sheldon, W. F., Horwitz, O., Kuo, P. T., Peirce, G., Zinsser, H. F., and Mead, J., Jr.: Studies of coronary disease in the experimental animal. II. Polarographic determinations of local oxygen availability in the dog's left ventricle during coronary occlusion and pure oxygen breathing, J. Clin. Invest. 30:932, 1951.
7. Sayen, J. J., Sheldon, W. F., Peirce, G., and Kuo, P. T.: Polarographic oxygen, the epicardial electrocardiogram and muscle contraction in experimental acute regional ischemia of the left ventricle, Circulation Res. 6:779, 1958.
8. Coffman, J. D., and Gregg, D. E.: Ventricular fibrillation during uniform myocardial anoxia due to asphyxia, Am. J. Physiol. 198:955, 1960.
9. Kazzaz, D., and Shanklin, W. M.: The coronary vessels of the dog demonstrated by colored plastic (vinyl acetate) injections and corrosion, Anat. Rec. 107:43, 1950.
10. Blair, E.: Anatomy of the ventricular coronary arteries in the dog, Circulation Res. 9:333, 1961.
11. Van Citters, R. L.: Work capacity of the left ventricle following ligation of the coronary artery, Am. Heart J. 58:391, 1959.
12. Senderoff, E., Wellberry, A. E., Kaneko, M., and Baronofsky, I. D.: Experiences with attempts at ventricular defibrillation in the presence of acute coronary occlusion, Ann. Surg. 151:191, 1960.
13. Cherbakoff, A., Toyama, S., and Hamilton, W. F.: Relation between coronary sinus plasma potassium and cardiac arrhythmia, Circulation Res. 5:517, 1957.
14. Wexler, J., and Patt, H. H.: Evidence that serum potassium is not the etiological agent in ventricular fibrillation following coronary artery occlusion, Am. Heart J. 60:618, 1960.
15. Stephenson, S. E., Jr., Cole, R. K., Parrish, T. F., Bauer, F. M., Jr., Johnson, I. T., Jr., Kochtitzky, M., Anderson, J. S., Jr., Hibbitt, L. L., McCarty, J. E., Young, E. R., Wilson, J. R., Meiers, H. N., Meador, C. K., Ball, C. O. T., and Meneely, G. R.: Ventricular fibrillation during and after coronary artery occlusion, Am. J. Cardiol. 5:77, 1960.
16. Harris, A. S.: Terminal electrocardiographic patterns in experimental anoxia, coronary occlusion and hemorrhagic shock, Am. Heart J. 35:595, 1948.
17. Dagher, I. K., and Clowes, G. H. A., Jr.: Failure of the circulation in acute hypoxia, Surgical Forum 42nd Clinical Congress, Chicago, American College of Surgeons 7:197, 1957.
18. Kardesch, M., Hogancamp, C. E., and Bing, R. J.: The effect of complete ischemia on the intracellular electrical activity of the whole mammalian heart, Circulation Res. 6:715, 1958.
19. Brooks, C. M., Gilbert, J. L., Lange, G., and Mazzella, H. M.: Changes in excitability and electrical response in areas of heart muscle made ischemic by coronary artery ligation, The Physiologist 2(3):17, 1959.
20. Harris, A. S., Bisteni, A., Russell, R. A., Brigham, J. C., and Firestone, J. E.: Excitatory factors in ventricular tachycardia resulting from myocardial ischemia. Potassium a major excitant, Science 119:200, 1954.
21. Beck, C. S.: Asphyxiated heart and ventricular fibrillation, Am. J. Physiol. 199:1245, 1960.

Progressive electrocardiographic changes associated with digitalis in the presence of complete A V heart block: an experimental study

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Previous work from this laboratory presented data which suggested that tolerance for digitalis in the animal with complete A V heart block does not differ significantly from that in the normal animal[1] Although digitalis intoxication has been cited as the most common cause of cardiac arrhythmias,[2] and has been discussed in detail by many authors[3-6] little attention has been paid to the electrocardiographic changes of digitalis cardiotoxicity in the presence of chronic complete A V heart block. Since A V dissociation and A V heart block occur as manifestations of digitalis intoxication one questions how experimental A V heart block might modify the electrocardiographic manifestations of digitalis cardiotoxicity We have attempted to show in dogs with surgically induced chronic complete A V heart block the sequential electrocardiographic alterations produced by digitalis.

Methods and materials

Complete heart block was surgically induced in 6 mongrel dogs which weighed between 9 1 and 10 9 kilograms using the method described by Taufic Bashour and Lewis.[7] Subsequently at least 3 weeks postoperatively when it was apparent that the animals had permanent heart block, yet appeared to be in good health a bioassay of digitalis was performed using the Magnus modification of the Hatcher Brody technique.[8] In a group of control dogs with normal A V conduction, the mean lethal dose of digoxin infused at a constant rate was found to be 0 293 mg kg

Experimental animals were lightly anesthetized with intravenous 6 per cent Nembutal and given positive pressure oxygen through an endotracheal tube with the aid of a mechanical respirator Blood for determinations of electrolytes was obtained by cannulization of the femoral artery and continuous electrocardiograms and blood pressures were recorded utilizing a Sanborn Twin Visocardiette. Digoxin † 0.293 mg /kg was diluted to 112 c.c. with 5 per cent glucose in water and infused at a rate of 1.25 c.c per minute with a con

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†Lanoxin (digoxin) injection [illegible] 2 c.c. ampule Burroughs, Wellcome & Company

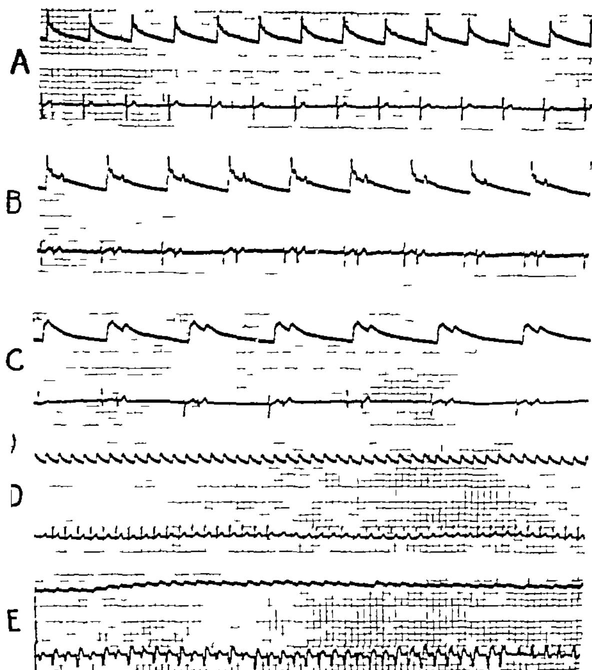


Fig. *1*. The top graph in each representative tracing is the record of blood pressure in the femoral artery. Each large square is equivalent in pressure to 25 mm. of mercury, and the base line coincides with the top of the lowest row of squares. Lead II of the electrocardiogram is recorded in the lower half of each strip. *A*, Control record. Complete A-V heart block. Atrial rate of 150 per minute. QRS of 0.06 sec. Blood pressure of 280/70 mm. Hg. *B*, After 0.052 mg./kg. of digoxin infused, premature nodal contractions in bigeminy. Basic ventricular rate *without extrasystoles is 31 per minute. Blood pressure of 320/60 mm. Hg. C*, After infusion of 0.229 mg./kg. of digoxin. Occasional premature nodal contraction. *D*, After infusion of 0.250 mg./kg. of digoxin, nodal tachycardia. Ventricular rate of 154 per minute. Atrial rate of 167 per minute. Blood pressure of 210/30 mm. Hg. QRS of 0.07 sec. *E*, After infusion of 0.297 mg./kg. of digoxin, ventricular tachycardia with electrical alternans (bidirectional ventricular tachycardia). Asystole occurred after 0.302 mg./kg. of digoxin was given.

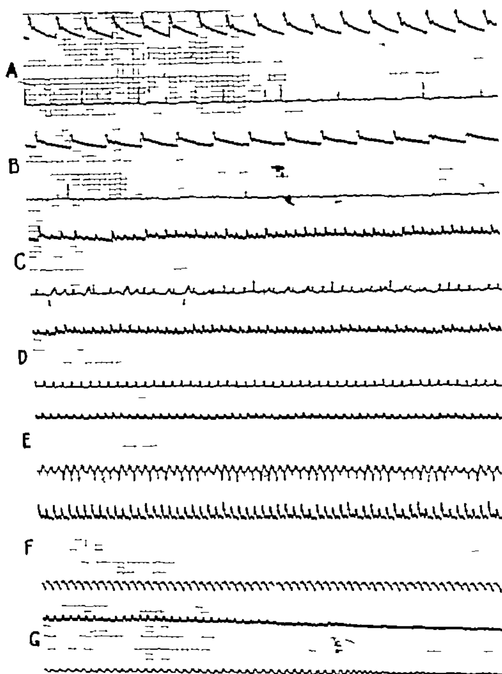


Fig. [illegible]. *A*, Control record. Atrial rate, 150/min. Ventricular rate, 56/min. QRS duration, 0.06 sec. BP 205/110 mm. Hg. Complete A-V heart block. *B*, After infusion of 0.154 mg./kg. of digoxin, some slowing of ventricular rate and atrial rate noted. Ventricular rate 44/min. Atrial rate 136/min. BP 210/95. *C*, With 0.236 mg./kg. of digoxin infused, frequent premature ventricular and premature nodal contractions. Average ventricular rate 167/min. Atrial rate 190/min. Average QRS, 0.06 sec. BP 200/110. *D*, After 0.246 mg./kg. of digoxin, BP is 130/115. Ventricular rate 200/min. A tachycardia characterized by widened QRS is observed. Complexes of similar configuration are also seen in ectopic beats in *C*. This suggests two possibilities: nodal tachycardia with aberrant conduction or ventricular tachycardia with a focus differing from that seen in *E*. *E*, With 0.277 mg./kg. of digoxin infused, ventricular tachycardia. Ventricular rate, 300/min. BP 130/115. *F*, After 0.299 mg./kg. of digoxin infused, ventricular tachycardia with widening of the QRS complex. Ven[illegible] 176/min. QRS 0.10 sec. BP 165/110. *G*, With 0.358 mg./kg. of digoxin infused [illegible] asystole.

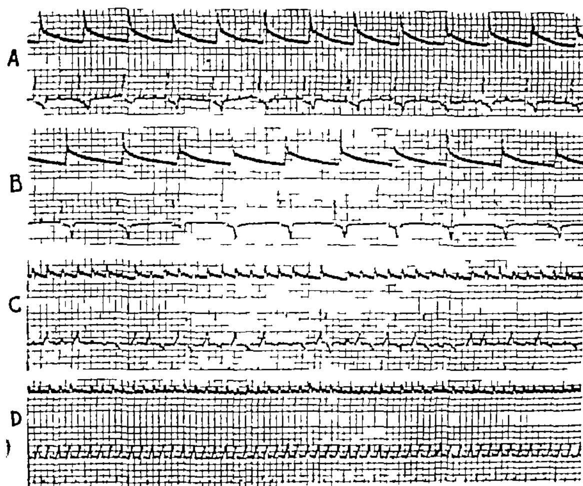


Fig 3,A D A Control record Complete A V heart block *Atrial rate of 166 per minute. Ventricular rate of* 2 per minute. Blood pressure of 280/60 mm. Hg QRS of 0 06 sec *B* With 0 157 mg /kg of digoxin infused, slowing of both atrial and ventricular rates with inverted P waves No appreciable change in QRS-T configuration Atrial rate of 13? per minute Ventricular rate of 35 per minute. Blood pressure of 280/60 *C* After 0 186 mg /kg of digoxin infused, premature nodal contractions with transient bigeminy Average ventricular rate of 130 per minute Blood pressure of 180/30 *D* After 0 209 mg./kg. of digoxin infused, nodal tachycardia. Ventricular rate of 188 per minute Primary blood pressure of 185/130 Secondary blood pressure of 150/120

stant rate infusion pump attached to a cannula in the femoral vein Increments of the same dilution were added where necessary to continue the experiment

Results

Changes observed in dogs during digitalis intoxication with chronic complete A V heart block are graphically illustrated in Figs. 1 3 and summarized in Tables IA IB and II

Ventricular slowing was the earliest electrocardiographic change noted in all animals although its onset varied with the administration of 0 042 to 0 240 mg /kg (7 to 48 per cent of the lethal dose) of digoxin This was often preceded by an increase in systolic blood pressure In 50 per cent of the animals ectopic nodal contractions followed ventricular slowing the onset varied from 0 052 to 0 259 mg kg (17 to 62 per cent of the lethal dose) of digoxin Nodal bigeminy and nodal tachycardia were also noted (Fig 1,*D*) and in 83 per cent of the animals ventricular ectopic beats occurred with 0 039 to 0.275 mg /kg (14 to 68 per cent of the lethal dose) of digoxin This was followed at 0 195 to 0.297 mg /kg (54 to 98 per cent of the lethal dose) of digoxin by ventricular arrhythmias predominantly ventricular tachycardia (Fig 2,*E* and *F*) In

most animals, QRS widening and aberration accompanied the tachycardia and was followed by ventricular fibrillation and death. A seizure characterized electrocardiographically by ventricular asystole with continuous regular atrial activity occurred in Dog No. 6 at 65 per cent of the lethal dose. This animal recovered spontaneously within 1 minute, exhibiting an idioventricular rhythm which was followed sequentially by ventricular tachycardia ventricular fibrillation and death (Fig 3,*E*)

Control electrolytes are recorded in Table II In 3 animals electrolytes were obtained at the time of QRS widening and showed a marked rise in serum potassium

Histologic examination of the septum in the region of the A-V node revealed suture material with surrounding fibrosis and granulomatous change. Toxic necrosis was not observed in the muscle.[7]

Discussion

Among the electrocardiographic signs of digitalis intoxication are varying degrees of heart block and A-V dissociation In a previous communication evidence that the lethal dose of digoxin was similar in both

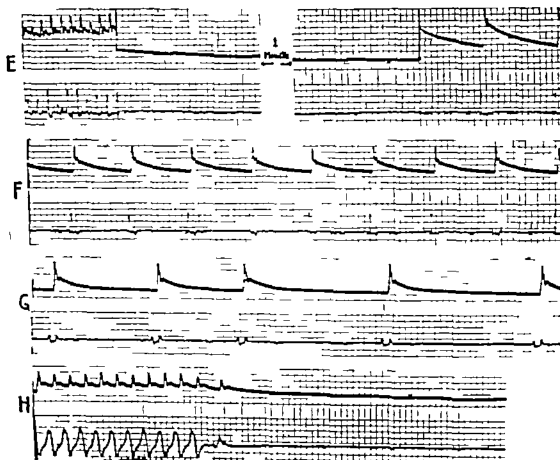


Fig 3,*E-H* *E*, With 0 230 mg /Kg. of digoxin infused, ventricular tachycardia followed by ventricular arrest lasting approximately 1 minute Atrial rate of 166 per minute. *F* After recovery from ventricular arrest, a slow idioventricular rhythm with 0.235 mg /Kg of digoxin infused. Atrial rate of 183 per minute Ventricular rate of 31 per minute Blood pressure of 230/100 mm. Hg *G* After 0 332 mg /Kg of digoxin, irregular slow idioventricular rhythm with QRS widening Inverted P waves also noted at regular intervals. Ventricular rate of 16 per minute (average). Atrial rate of 27 per minute. Blood pressure of 250/?0 *H* After 0 343 mg./Kg of digoxin, ventricular flutter is followed by ventricular standstill. Atrial activity is still present (inverted P waves) at same rate as in *F* Blood pressure fell to 0/0 with ventricular arrest.

Table IA. Occurrence of digoxin-induced arrhythmias

Dog	Ventricular slowing	Premature nodal extractions	Nodal bigeminy	Premature ventricular contractions	Ventricular bigeminy	Changing atrial pacemaker	Nodal tachycardia
1	0.013 (7%)	0.052 (17%)	0.065 (22%)				0.244 (81%)
2.	0.031 (16%)			0.039 (21%)			
3	0.154 (11%)	0.212 (59%)		0.236 (66%)			0.246 (69%)
4.	0.240 (48%)	0.259 (62%)		0.275 (68%)			
5.	0.052 (14%)			0.052 (14%)	0.081 (22%)	0.160 (43%)	
6.	0.144 (42%)			0.186 (54%)		0.157 (46%)	

Table IB

Dog	Ventricular tachycardia	Adams-Stokes	Ventricular tachycardia with QRS widening	Ventricular flutter	Ventricular fibrillation	Idioventricular rhythm	Asystole
1	0.297 (98%)						0.302 (100%)
2.						0.144 (73%)	0.191 (100%)
3	0.277 (78%)		0.299 (84%)	0.358 (100%)	0.358 (100%)		0.358 (100%)
4	0.275 (68%)		0.413 (99%)		0.414 (100%)		0.414 (100%)
5	0.195 (54%)		0.246 (68%)		0.367 (100%)		0.367 (100%)
6.	0.209 (56%)	0.230 (68%)	0.332 (96%)	0.343 (100%)	0.343 (100%)	0.235 (70%)	0.348 (100%)

Types of alterations in rhythm are correlated with the dose of digoxin. All values except those in per cent are in milligrams per kilogram of dog. Percentages are per cent of lethal dose.

Table III. Electrolyte data on dogs with A-V heart block given digoxin

Electrolyte	Dog 2	Dog 3	Dog 4		Dog 5		Dog 6	
	Control	Control	Control	Repeat	Control	Repeat	Control	Repeat
Na (mEq./L.)	140	141	144.5	135	131.5	125.5	144.5	130
K (mEq./L.)	4.66	4.0	3.58	6.14	3.56	6.60	3.4	10.44
Cl (mEq./L.)	120	115	127.5	125	130	127.5	125	122.5
HCO_3 (mEq./L.)	19	22	18.0	11.0	14.0	13.0	10.0	8.0
Ca (mg. %)	8.16	8.0	7.3	7.9	7.6	8.0	8.0	8.8
P (mg. %)	3.3	3.78	4.41	4.41	3.6	2.95	4.64	3.82
Mg (mg. %)	2.3	—	—	—	3.16	2.9	2.43	2.67

Control studies were made before infusion of digoxin was started. Repeat studies were made at time of QRS widening, usually just prior to terminal phase.

normal animals and those with complete heart block was presented.[1] It was also observed that the onset of nodal and ventricular arrhythmias in each group occurred over approximately the same percentage range of the lethal dose of digoxin. In addition, nodal tachycardia seemed to appear in animals with heart block at a dosage which grossly approximated that which produced A-V block and A-V dissociation in the control group, although the ranges over which these changes occurred were quite broad.

There did not seem to be any correlation between the rapidity with which arrhythmias appeared and the degree of digitalis tolerance measured by the lethal dose. Extrasystoles, frequently beginning early in toxicity, occasionally progressed rapidly to ventricular tachycardia. Ventricular slowing occurred in all animals prior to any of the aforementioned manifestations of intoxication.

QRS widening which appeared terminally in our experiments seemed to be associated with an elevated serum potassium. This elevation of the serum potassium is not readily explained although Lown, Black, and Moore[12] have shown that digitalization in the presence of acidosis may cause significant elevation of potassium. Moreover, recent work by Muller, De Leon, and Bellet[11] has demonstrated an increased sensitivity to potassium in dogs with complete heart block. Such a cause-effect relationship is difficult to establish from our data. As is characteristic of digitalis poisoning, most of our experiments were terminated by ventricular fibrillation.

Conclusions

1. During a bioassay of digitalis in mongrel dogs with surgically induced chronic complete A-V heart block, the electrocardiographic events of digitalis intoxication were studied.

2. Many familiar signs of cardiotoxicity appeared, including bigeminy and nodal and ventricular tachycardia. Disturbances in A-V conduction which are characteristic of digitalis intoxication were not observed since conduction pathways had been surgically interrupted and propagation of atrial impulses to the ventricles was impossible.

3. Except for a superimposed chronic conduction disturbance in the experimental group, the evolution and features of digitalis intoxication in normal control animals and in animals with heart block seemed to be similar.

REFERENCES

1. Nonkin, P. M., Bennett, L. D., Becker, D. J., and Wasserman, F.: The use of digitalis in chronic complete A-V heart block, Am. J. Cardiol. (to be published).
2. Burwell, W. B., and Hendrix, J. P.: Digitalis poisoning, Am. J. Med. 8:640, 1950.
3. Crouch, R. B., Herrmann, G. R., and Hejtmancik, M. R.: Digitalis intoxication, Texas J. Med. 52: 14, 1956.
4. Von Capellar, D., Copeland, G. D., and Stern, T. N.: Digitalis intoxication: clinical study of 148 cases, Ann. Int. Med. 50:869, 1959.
5. Shrager, M. W.: Digitalis intoxication. A review and report of 40 cases with emphasis on etiology, A.M.A. Arch. Int. Med. 100:881, 1957.
6. Friedberg, C. K., and Donoso, E.: Arrhythmias and conduction disturbances due to digitalis, Prog. Cardiovas. Dis. 2:408, 1960.
7. Dearing, W. H., Barnes, A. R., and Essex, H. E.: Experiments with calculated therapeutic and toxic doses of digitalis, AM. HEART J. 25:648, 1943.
8. Taube, M., Bashour, F. A., and Lewis, F. J.: Production of heart block in dogs under direct vision, Surg. Forum 6:96, 1955.
9. Burn, J. H.: Biological standardization, London, 1950, Oxford University Press, p. 298.
10. Rodensky, P. L., and Wasserman, F.: (In press).
11. Muller, O. F., De Leon, A. C., Jr., and Bellet, S.: The effect of hyperpotassemia on the idioventricular pacemaker in complete A-V heart block and comparison with its effect on the heart rate in normal sinus rhythm. An experimental study in dogs, Am. J. Cardiol. 7:817, 1961.
12. Lown, B., Black, H., and Moore, F. D.: Digitalis, electrolytes, and the surgical patient, Am. J. Cardiol. 6:309, 1960.

Case reports

Anomalous origin of coronary artery from pulmonary artery masquerading as mitral insufficiency

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The diversity of the clinical syndromes associated with an anomalous origin of a coronary artery from the pulmonary artery is generally recognized. The clinical syndrome of infantile angina or its equivalent, with the electrocardiogram indicating myocardial ischemia or infarction, is now, however, appreciated to be the unusual form of the clinical picture. More often there is evidence of early and progressive enlargement of the left ventricle with evidence of heart failure, and the differential diagnosis lies frequently between endocardial sclerosis and anomalous coronary artery.

In the case to be described, mitral insufficiency was the prominent feature of the clinical state, and this caprice of the disease would seem to be unique. Of additional interest in regard to the coronary hemodynamics were conjectures concerning the effects of the secondary pulmonary hypertension related to chronic left ventricular failure. In particular, an insignificant pressure gradient would be expected across the collaterals in the two coronary systems in the period of observation allowed us.

The diagnosis of endocardial sclerosis routinely calls to mind the possibility of an abnormal coronary circulation. However, in the present instance such thoughts never were given credence because of the evidence of gross mitral insufficiency.

An additional point of interest in the case was the arrangement of the coronary arteries, which had favorable aspects in regard to possible successful surgical correction because the anomalous coronary was contiguous to the aorta.

Report of case

A 14-year-old boy was referred to the Mayo Clinic in 1956, *for evaluation of his heart disease.* The referring physician mentioned congenital aortic stenosis and ventricular septal defect as possibilities. The patient's birth had been normal, and the neonatal course was without complications, as was the development in early childhood. The physician reported that a heart murmur had been present when the boy was routinely examined at 3 years of age. In later childhood he had had definite exercise intolerance because of effort dyspnea, but he had never had any chest pain.

When examined the patient weighed 80 pounds and his blood pressure was 110 mm. of mercury systolic and 75 diastolic. He had a Grade 2 pansystolic murmur (graded on the basis of 1 to 4) which was maximal at the apex, and a faint early diastolic murmur in the same area. The systolic murmur was heard well into the anterior part of the axilla and toward the sternum. The pulmonary *component of the second sound* was markedly accentuated. On the basis of clinical examination

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It was believed that the patient had disease of the mitral valve and pulmonary hypertension, but the nature of the mitral disease was conjectural. The heart was moderately enlarged (Fig. 1), and the electrocardiogram (Fig. 2) showed evidence of left ventricular hypertrophy and left atrial enlargement.

The right and left sides of the heart were catheterized (Table I), and the basic interpretations of the catheterization data were pulmonary hypertension, left ventricular failure or decreased left ventricular compliance, or both, mitral insufficiency and slight mitral stenosis. It was noted that the v wave of the "wedged pressure" did not strongly support mitral insufficiency. The cardiac output was normal, and possibly related to this was the significant presystolic (end-diastolic) increase in left ventricular pressure associated with left atrial contraction.

In a retrospective study of the data there was no evidence of any arterialization in the pulmonary artery although frequent oximetric determinations of the saturation in that vessel had been made.

After initial investigation at the clinic the boy's condition was followed by correspondence. It was reported that atrial fibrillation appeared in May 1958, and that he had temporarily manifested signs of frank heart failure. Under treatment with digitalis and chlorothiazide (Diuril) his condition improved to its previous state, and he was able again to perform moderate physical activity. It was thought that surgical therapy should be given greater consideration, although there was uncertainty as to the nature of the valvular defect because endocardial sclerosis was suspected.

The scheduling of an operation was deferred on several occasions, but finally it seemed proper to attempt repair of the valve. This was done on June 28, 1960. Whole-body perfusion with a pump-oxygenator was used. The marked enlargement of the heart was confirmed; all chambers participated in the enlargement. The left atrium was huge, and the pressure in it was 49/20 mm. Hg, whereas the pressure was 90/13 in the left ventricle, 68/3 in the right ventricle, and 11/3 in the right atrium. There was obvious severe incompetence of the mitral valve, with the regurgitant jet being directed toward the left shoulder and, thus, predominantly toward the left atrial appendage. The mitral annulus was dilated, and the surgeon reported that it would admit 3½ fingers with ease. The anterior leaflet seemed to be of normal appearance, whereas the posterior leaflet seemed to be definitely shortened. There was no recognized evidence of endocardial sclerosis. Under conditions of ischemic cardiac arrest, a rigid baffle in the form of an Ivalon roll was inserted into an area occupied by the posterior leaflet. After the repair, which seemed to be adequate, the left atrial pressure was 34/19 mm. Hg at the time the left ventricular pressure was 94/8.

At operation no anomaly of the coronary arteries was searched for or recognized. Such a search might have been difficult at best as judged from later examination of the coronary arteries.

The immediate postoperative course was smooth and uneventful. The heart was less overactive and the intensity of the systolic murmur was decreased. It was thought justifiable to conclude that the hemodynamics and, likewise, the prognosis had been improved. Approximately 3 weeks after operation, however, signs of heart failure developed, but despite this the condition of the patient again improved and he was able to return to moderate activity without respiratory distress. The improvement, however, was rather short lived, and by November, 5 months after operation, he had severe disability although no frank edema, syncope, or chest pain. He died suddenly on the eve of a scheduled routine re-evaluation.

Postmortem examination revealed a rather thin boy 16 years of age. The relevant findings were confined to the heart. The heart weighed 540 grams, with the main mass being in the left ventricle. The right ventricle was dilated, as were the two atria. The repair on the mitral valve was well healed although the Ivalon roll had apparently rotated backward over the top of the ventricular wall so that it no longer gave significant reinforcement or increased length to the posterior leaflet. The left ventricular wall was grossly scarred, although not thinned. The finding of note was the origin of the left coronary artery from the pulmonary artery. This vessel arose from the posterior aspect of the pulmonary artery well above the commissure between the right and left posterior leaflets of the pulmonary valve, and gave rise to the usual anterior and circumflex branches. Its origin thus was within a few millimeters of the anterior aortic wall, which explained the cryptic nature of its origin at the time of operation. At the same time it introduced the technical problem of how readily it might possibly have been transplanted to the aortic wall. It is believed that even if this had been possible, the destruction of the left ventricular muscle had progressed to the point at which the procedure would have been ineffective in restoring adequate function to the heart.

*Table I. Cardiac catheterization data in 1956**

	Pressure (mm. Hg)	Oxygen saturation (per cent)
Right ventricle	75/2-7	71
Right atrium	7/-1	71
Coronary sinus	—	21
Pulmonary artery	75/48	69
Aorta	101/73	—
Left atrium	25/19-22	96
Left ventricle	114/7 20	—

Cardiac output 4.5 L. per min.
Cardiac index 3.6
Total pulmonary resistance 1,070 dynes sec. cm.
Pulmonary arteriolar resistance 480 dynes sec. cm.
Dye curves: Disproportionate prolongation of disappearance slope

*The collaboration of Dr. Earl H. Wood in the review and interpretation of the data is gratefully acknowledged.



Fig. 1. Roentgenographic appearance of heart: a, August 1956; b and c, July 1959. Enlargement of heart is particularly suggestive of left atrial and left ventricular enlargement.

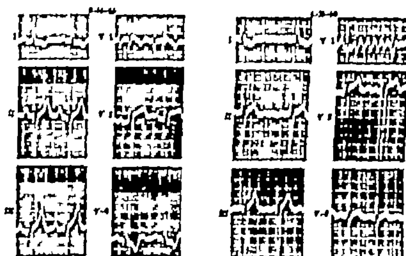


Fig. 2. Electrocardiogram taken in 1956 and 1960.

The endocardium was moderately thickened but the thickening was not the thick fibrous type of the primary type. Destruction of the heart muscle evident microscopically was most marked (Fig. 3) and the structure of the pulmonary artery in relationship to the aorta indicated that the pulmonary hypertension had been acquired in childhood and that it had not been present since birth. Grossly no anastomoses could be seen between the two coronary systems; indeed, the vessels seemed to be quite sparse in relationship to the mass of the ventricular muscle. In view of the possibility of retrograde flow in the left coronary artery, sections of the right and left coronary arteries taken a few millimeters from their origin were studied in regard to relative thickness of their walls. The left (anomalous) coronary which arose from the pulmonary artery showed the thinner media (Fig. 4).

Comment

The proper diagnostic procedure for patients who are suspected of having anomalous coronary arteries is not established. We have made exploratory ventures into the injection of dye into the aorta with sampling at the pulmonary artery and into selective angiography of the pulmonary artery. We believe as do others that at present the best approach would be that of aortography, which would give the evidence in a negative way, that is, it would show absence of a coronary artery and occasionally evidence of retrograde filling. If the clinical picture fitted

a further procedure might be outlined on an individual basis. It is not believed that in this case there would be characteristic thinning in the left ventricular wall such as might be revealed by an angiocardiogram as in the infants reported on by Lang and co-workers.[8] In retrospect, the one electrocardiogram in 1956 (Fig 2) might have given the clue that there was more ischemic damage than could be readily accounted for on the basis of endocardial sclerosis. In the 1958 period some epigastric pain had been reported and right hypochondrial distress was believed at the time to be related to congestion of the liver which interpretation still seems to be probably the correct one

The present availability of direct surgical treatment of cardiac defects has focused interest on anomalously originating coronary arteries. Transplantation of the anomalous origin of an artery production of pulmonary arterial narrowing and ligation of the anomalous artery near its origin have been utilized in treatment It is an ancient suggestion that the blood flow in an anomalous left coronary might be in a retrograde direction and this concept has been reviewed in detail by Edwards,[3] with the suggestion by him and one of us (H B B) that coronary circulation would be improved by ligation of the anomalous artery at its origin This procedure was independently recommended by Case and co-workers. Evidence of retrograde flow in arteries of anomalous origin as gained in the operating room has been convincingly demonstrated by Rowe and Young [9] Successful ligation of an artery in an infant has been reported by Hung and Walsh[7] the infant survived 11 months, but significantly postmortem examination showed that no gross infarct or scarring had followed the ligation. Pertinent however is the case of an infant reported by Kuzman and co-workers [6] wherein temporary occlusion of an anomalous vessel caused cardiac dilatation and heart block.

In regard to the specific problems presented by our patient it is noteworthy that in Keith's review[4] of anomalous origin of the left coronary artery there is no record of patients with loud murmurs, nor was murmur a prominent finding in the group of infants reported on by Sabiston and co-workers.[10] It can be concluded that not only is mitral insufficiency a rare manifestation but also that it would be unlikely to be a presenting sign in infancy In this regard a parallelism might be drawn with the mitral insufficiency that occasionally complicates ventricular septal defect as an

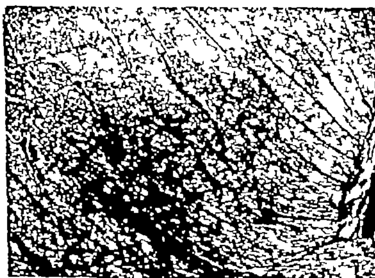


Fig 3 Diffuse fibrosis of left ventricular myocardium in portion of myocardium normally supplied by left coronary artery (elastic tissue van Gieson stain; ×25).



Fig. 4. *a*, Right coronary artery. *b*, Left (anomalous origin) coronary artery. A few thin elastic lamellae are present and the wall is thinner than normal. Elastic tissue–Gieson stain (×75) used in each instance.

unusual consequence of left ventricular dilatation in teen-age children.

In our case cardiac catheterization did not reveal any "arterialization" in the pulmonary artery. In contradistinction in a patient of approximately the same age reported on by Lampe and Verheugt[7] an increase in oxygen content (0.5 volume per cent) was repeatedly found in the pulmonary artery. An angiocardiogram showed a tortuous dilated right coronary artery and retrograde filling of the left coronary artery. From the angiocardiogram shown in their article the left coronary artery could have arisen from the posterior wall of the pulmonary artery as in our case. Jurishica[4] has reported a case in which the anatomy of the coronary vessels was apparently similar to that in our case and on the basis of a review of the cases in adults (ages 16 to 60 years) he reported that in 45 per cent the anomalous vessel was thin and veinlike.

Summary

An adolescent boy with the presenting problem of gross mitral insufficiency was found to have the basic abnormality of a left coronary artery arising from the pulmonary artery. From the physiologic and pathologic data collected no conclusion could be reached in regard to the direction of blood flow in the anomalous vessel. Gross and extensive myocardial fibrosis was present. The mitral incompetence appeared to be related primarily to the enlargement of the left ventricle and the mitral annulus.

Addendum

Since the foregoing paper was prepared an additional report has appeared in which the problem presented by a patient with an anomalous coronary artery was quite similar to the one presented in our case and surgical therapy to relieve the mitral insufficiency also was carried out.[11]

REFERENCES

1. Case R. B., Morrow A. G., Stainsby W., and Nestor J. O.: Anomalous origin of the left coronary artery: the physiologic defect and suggested surgical treatment, Circulation 17:1062, 1958.
2. Edwards, J. E.: Anomalous coronary arteries, with special reference to arteriovenous-like communications (Editorial), Circulation 17:1001, 1958.
3. Hung, W., and Walsh, B. J.: Anomalous left coronary artery arising from the pulmonary artery: report of a case diagnosed clinically and operated upon, with autopsy findings, Clin. Proc. Child. Hosp. Washington, D.C. 16:228, 1960.
4. Jurishica, A. J.: Anomalous left coronary artery, adult type, Am. Heart J. 54:429, 1957.
5. Keith, J. D.: The anomalous origin of the left coronary artery from the pulmonary artery, Brit. Heart J. 21:149, 1959.
6. Kittman, W. J., Yoshida, A. S., and Carmichael, D. B.: Anomalous left coronary artery arising from pulmonary artery, Am. Heart J. 57:336, 1959.
7. Lampe, C. F. J., and Verheugt, A. P. M.: Anomalous left coronary artery. Adult type, Am. Heart J. 59:769, 1960.
8. Lang, E. K., Phillips, L. A., and McAfee, J. G.: Angiocardiographic features of the Bland-White-Garland syndrome, Am. J. Roentgenol. 80:381, 1958.
9. Rowe, G. G., and Young, W. P.: Anomalous origin of the coronary arteries with special reference to surgical treatment, J. Thoracic & Cardiovas. Surg. 39:777, 1960.
10. Sabiston, D. C., Pelargonio, S., and Taussig, H. B.: Myocardial infarction in infancy: the surgical management of a complication of congenital origin of the left coronary artery from the pulmonary artery, J. Thoracic & Cardiovas. Surg. 40:321, 1960.
11. Usman, A., Fernandez, B., Cricchio, J. F., and Nichols, H. T.: Aberrant origin of left coronary artery combined with mitral regurgitation in an adult, Am. J. Cardiol. 8:130, 1961.

Cardiac output and Albright's syndrome

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Paget s disease is a condition commonly associated with a high cardiac output The physiopathologic disturbance has been ascribed to increased vascularization of the diseased bone. High cardiac outputs are also observed in anemia, thy*rotoxicosis, arteriovenous fistulas* beriberi cor pulmonale and in some cases of liver disease Occasionally no obvious etiology can be discovered [1]

As far as we know there is no observa in the literature of a similar disturb- e in Albright s syndrome.

Case report

L. W., a 12 year-old bedridden girl, presented multiple café-au-lait pigmented spots distributed on the bdomen, the back, and the neck. Menstruation had appeared when she wa 6 weeks of ge. When she was 3½ years old, secondary sexual features were manifest enlargement of the breasts, growth of pubic and axillary hair The x-ray ex mination showed thickening and cystic formation of the base of the skull, which had a fuzzy appearance and a generalized involvement of the bones, especially the pel is. The diagnosis of Albright disease was made Spontaneous fractures of the limbs occurred Bone grafts were attempted unsuccessfully

Blood levels of Ca h., N and proteins were within normal limits. Total cholesterol was elevated on several occasion 373 394 and 258 mg per cent Hemoglobin was 13 4 Gm per cent Blood counts were normal (red blood cells 4,220 000 white blood cells 5,200 neutrophils 53 5 per cent eosinophils 0.5 per cent basophils none monocytes 11.5 per cent lymphocytes 34 5 per cent). The alkaline phosphatase was elevated (30 units). Urinary *levels of 17 ketosteroids, 17 hydroxycorticoids* were normal, as was the gonadotrophin excretion. A biopsy of the right hip showed important changes in the bone structure, which macroscopically had a *high blood content* Besides marked osteoclastic changes and cysts, microscopic examination revealed a severe fibromatosis of the marrow and osseous metaplasia. The vascularization wa also ery much modified the arterioles were more numerous than normally and the arterial capillaries were dilated and often arranged in clumps. The enous sinuses were enlarged, and sometimes formed bloody pools which measured up to 400 to 600 μ in diameter (Fig 1).

Her cardiac condition had drawn attention already in 1950, when murmur was heard. The patient had no history of rheumatic fever chorea d phtheria, or scarlet fever In March 1958 a soft continuous murmur was aud ble at the base and over the left sternal border There were electrocardiographic signs of left entricular hypertrophy and the x-ray film showed that the heart was markedly increased in size In January 1959 a systolic murmur was heard The electrical and radiologic signs of left entricular hypertrophy which previously *had been observed had increased. The blood* pressure was 120/40 mm. Hg with a pulsus altus et celer There was no sign of right heart failure.

The patient was re-examined at the Centre de *Cardiologie of the University of Geneva* Hospital in December 1960 She wa pale and seemed to be chronically ill Her height was 139 cm., and she weighed 83.5 pounds. Deformities of the extremities were noted. The lungs were clear there wa no cyanosis and no peripheral edema but there w a

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*The endocrine aspect of this case and the therapeutic implications were discussed by Ducommun, Rutishauser and Müller in *Médecine et Hygiène* 18 194, 1960



Fig. 1. A. Fibromatous and osseous metaplastic bridges with irregular areas of calcification (X48). B. Dilated arteriole and capillaries (X85). C. Fibrous metaplastic bone seen in birefringent light (X90).

slight hepatomegaly. The cardiac evaluation showed slight right and left ventricular heave; there was no thrill; the sounds were normal; a systolic murmur Grade 1 was audible on the precordium, with maximum at the first left intercostal space and at the apex, radiating toward the neck. Careful auscultation over the body did not disclose any murmur which suggested an arteriovenous fistula. A phonocardiogram confirmed the findings: the murmur was holosystolic only. In spite of the fact that it seemed to persist after the second sound in the left subclavicular area. An x-ray film of the chest (Fig. 2) revealed a marked kyphoscoliosis of the thoracic spine and an increased cardiac size, with enlarged left and right ventricles. The electrocardiogram (Fig. 3) showed a sinus rhythm with a rate of 85. There was left axis deviation, and left ventricular hypertrophy was indicated by increased voltages on the left precordial leads.

Pulmonary functions (Dr. Moret's laboratory) showed a 28 per cent decrease in the ventilatory reserve. Vital capacity was 2,190 c.c. (77 per cent of the normal), and maximum expiratory volume was 1,890 L. per second (92 per cent of the normal). The ratio of maximum expiratory volume to vital capacity was 86 per cent.

In order to rule out congenital defect, right heart catheterization was performed on Dec. 12, 1960 (Table I). The patient had received 100 mg. of Luminal as premedication and was adequately sedated. No evidence of a left-to-right shunt could be found at any level; samples of blood from the left pulmonary artery did not show any oxygen step-up. The venous blood saturation was slightly elevated, and there was a moderate arterial desaturation (91.5 per cent). Pulmonary capillary, pulmonary arterial, and right ventricular pressures were elevated. The small, insignificant gradient recorded across the pulmonary valve was considered to be of the functional, high output type. The cardiac output, measured by the Fick method, was indeed considerably increased (10.3 and 11.0 L.



Fig. 2. Chest x-ray film showing cardiac enlargement and kyphoscoliosis.

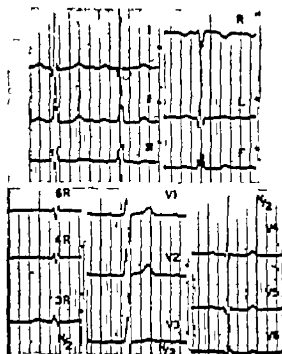


Fig. 3. Electrocardiogram showing left ventricular *hypertrophy*

per minute, with an average of 10.65 L. per minute), and the cardiac index was 8.8 L. per minute per square meter of body surface area.

The oxygen consumption was elevated and the arteriovenous difference narrowed. The pulmonary arteriolar and the systemic vascular resistances were low.

Discussion

Generalized osteitis fibrosa which is accompanied by an elevated cardiac output produces an increased ventricular load. Edholm and associates[2] were the first to measure cardiac output in Paget's disease and to observe in one case a considerable augmentation (13.3 L. per minute). Howarth[3] reported 13 cases of osteitis fibrosa; right heart catheterization was performed in 12 subjects with active lesions. Cardiac output was found to be normal in patients who had levels of alkaline phosphatase below 45 units, or in whom less than 35 per cent of the skeleton was involved. The mechanism and incidence of cardiovascular changes in Paget's disease was investigated by Sornberger and Smedal.[4] They emphasized the difficulty in appreciating alterations due to the disease because of concomitant atherosclerotic lesions in the same age group and because of the effect of the restriction of physical activity on the cardiac symptoms. These authors suggested that cardiac failure was due to an increased work load and to more severe atherosclerosis in Paget's disease. Lequime and Denolin[5,6] studied the effect of exercise on cardiac output and found that at rest there was no significant elevation whereas during exercise there was an abnormal increment in cardiac output in patients with osteitis fibrosa. Rapaport and associates[7] investigated the effect of cortisone treatment in 6 patients with extensive Paget's disease and found that high doses of cortisone produced reduction to normal levels of previously elevated cardiac output and parallel changes in the level of alkaline phosphatase.

After extensive review of the literature[8-23] we were unable to find any reference to cardiac output in cases of Albright's syndrome. However, the description of the first autopsy case of this syndrome[24] is suggestive: the 11-year-old child had marked and diffuse bone disease; the right ventricle measured 3 to 5 mm. and the left ventricle was 14 to 18 mm. in thickness. The heart weight (300 grams) seemed to be increased in relation to body size. Stauffer, Arbuckle and Aegerter[19] reported in 1941 a case of polyostotic fibrous dysplasia in a 19-year-old boy who had extremely severe involvement of the left side and cutaneous pigmentation; multiple congenital arteriovenous aneurysms in the left upper extremity were associated with palpable thrills and audible murmurs. The heart was enlarged clinically and on x-ray film, but the electrocardiogram was normal. Cardiac output was not measured, but it may have been elevated since venous oxygen saturation in the left forearm was 90.2 per cent as compared with 34.8 per cent in the right side. However, in their case the congenital arteriovenous aneurysm and not the Albright syndrome or the association of both might have produced an increased cardiac output.

Our patient had no auscultatory evidence of arteriovenous fistulas, no signs of thyrotoxicosis, beriberi, or liver disease, and a low normal blood count. She had only a moderate impairment of pulmonary functions, which can hardly be held solely responsible for her markedly increased

cardiac output the elevated pulmonary capillary pressure, in the absence of mitral disease suggests left ventricular failure Unfortunately pulmonary participation in the hemodynamic changes cannot be totally ruled out. Our patient presented the typical clinical picture of Albright's syndrome precocious puberty pigmentations and bone lesions. The severe and generalized involvement of the skeleton (pelvis, femurs, skull spine and tibias, in this order) was confirmed by numerous fractures, and proved histologically by several bone biopsies which showed marked changes in vascularization Rutishauser and associates[17] have demonstrated that in Paget's disease the arterioles of bone are dilated and more numerous. In their study there were per square centimeter 8 arterioles with a diameter greater than 15μ, as compared to 5 in the normal In the present case we counted 9 arterioles, several of which reached 75μ in diameter arborization of the arterial capillaries could be seen and there were venous sinuses which formed huge bloody pools which were as much as 600μ in diameter Thus this vascularization is very similar to that of the bones in patients with Paget's disease. We conclude therefore in this case, as Rutishauser and associates did in theirs that the vascular alterations can explain the decreased resistance, the elevation of blood flow in the diseased bone, and consequently the increased cardiac output in the more severe forms of the disease.

Summary

A case of Albright's syndrome in a 12 year-old girl is reported The patient was found to have a markedly increased cardiac output (10.6 liters per minute) with a cardiac index of 8.8 liters per minute per square meter of body surface area Although cor pulmonale cannot be completely ruled out as a factor it is suggested

Table I Catheterization data

	Oxygen content (vol. %)	Saturation (%)	Pressures (mm. Hg)	
			Systolic/diastolic	Mean
Superior vena cava	14.0	76	—	—
Right auricle	14.2	77		
	14.0	76	—	6
	14.0	76		
Right ventricle	13.85	75		
	14.0	76	56/7	—
	13.9	75.5		
Pulmonary artery (right)	14.2	77		
	14.0	76		
			46/18	27
(left)	13.9	75.5		
	14.2	77		
Pulmonary wedge	—	—	—	16
Femoral artery	16.9	91.5	140/80	100

Heart rate		100
Oxygen consumption (c.c./min.)		295
Cardiac output (L./min.)	11.0	10.3
Cardiac index—average (L./min./M²)		8.8
Pulmonary arteriolar resistance (dynes sec cm⁻⁵)		81
Total pulmonary resistance (dynes sec cm.⁻⁵)		203
Systemic vascular resistance (dynes sec cm.⁻⁵)		707

that the mechanism responsible for the hemodynamic changes may be comparable to that seen in Paget's disease. The very severe involvement of the bones observed in this patient and confirmed by repeated biopsies may lead to a similar high cardiac output state. We hope that future studies of this disease will help to clarify this point.

Addendum

After our paper had been submitted for publication an abstract by McIntosh and associates[28] was brought to our attention. These authors have observed similar changes in Albright's syndrome when the skeletal involvement was extensive enough.

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REFERENCES

1. Brachfeld, N., and Gorlin, R.: Idiopathic hyperkinetic state: a new clinical syndrome, Brit. Heart J. 22:353, 1960.
2. Edholm, O. G., Howarth, S., and McMichael, J.: Heart failure and bone blood flow in osteitis deformans, Clin. Sc. 5:249, 1945.
3. Howarth, S.: Cardiac output in osteitis deformans, Clin. Sc. 12:271, 1953.
4. Sornberger, C. F., and Smedal, M. I.: The mechanism and incidence of cardiovascular changes in Paget's disease: a critical review of the literature with case studies, Circulation 6:711, 1952.
5. Lequime, J., Denolin, H., and Vernory, A.: The circulation in the course of Paget's disease, Acta cardiol. 7:319, 1952.
6. Lequime, J., and Denolin, H.: Circulatory dynamics in osteitis deformans, Circulation 12:215, 1955.
7. Rapaport, E., Kuida, H., Dexter, L., Henneman, P. H., and Albright, F.: The cardiac output in Paget's disease before and after treatment with cortisone, Am. J. Med. 22:252, 1957.
8. Albright, F., Butler, A. M., Hampton, A. O., and Smith, P. H.: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females, New England J. Med. 216:727, 1937.
9. McCune, D. J.: Osteodystrophia fibrosa, Am. J. Dis. Child. 54:806, 1937.
10. Stauffer, H. M., Arbuckle, R. K., and Aegerter, E. E.: Polyostotic fibrous dysplasia with cutaneous pigmentation and congenital arteriovenous aneurysms, J. Bone & Joint Surg. 23:323, 1941.
11. Osgood, E. C.: Polyostotic fibrous dysplasia and osteopathia condensans disseminata, Am. J. Roentgenol. 56:174, 1946.
12. Berardinelli, W.: Two cases of Albright's syndrome observed in Brazil, J. Clin. Endocrinol. 10:1499, 1950.
13. Gray, L. G.: Sexual precocity in females, Pediatrics 8:654, 1951.
14. Bölke, E.: Über einen Fall von Albrightschem Syndrom, Ärztl. Wchnschr. 6:451, 1951.
15. Hibbs, R. E., and Rush, H. P.: Albright's syndrome, Ann. Int. Med. 37:587, 1952.
16. De Salcedo, I., and Almeida, V. C.: Albright's syndrome, Gaz. méd. port. 6:623, 1953.
17. Dechaume, M., Albeaux-Fernet, M., Gefinet, M., and Payen, J.: Albright's syndrome (study apropos of a case), Presse méd. 62:1787, 1954.
18. Laroche, C.: La maladie d'Albright, Semaine hôp. Paris 30:2757, 1954.
19. Aarlien-Soborg, L., and Iversen, T.: Albright's syndrome, Acta paediat. 45:558, 1956.
20. Peterman, M. G.: Polyostotic fibrous dysplasia, J. Pediat. 49:719, 1956.
21. Davies, M. L., and Yardley, S. H.: Fibrous dysplasia of bone, Am. J. M. Sc. 234:590, 1957.
22. Salvi, F.: Sindrome di Albright (presentazione di un caso), Riv. Ostet. ginec. 12:345, 1957.
23. Bordet, S., and Devriendt, A.: Dysplasie fibreuse polyostotique ou syndrôme d'Albright, Acta paediat. belg. 12:21, 1958.
24. Jesserer, H.: Erkrankungen und Probleme aus den Grenzgebieten der Inneren Medizin, Med. Klin. 55:225, 1960.
25. Jain, S. R., and Rangam, C. M.: Polyostotic fibrous dysplasia, J. Indian M. A. 34:451, 1960.
26. Sternberg, W. H., and Joseph, V.: Osteodystrophia fibrosa combined with precocious puberty and exophthalmic goiter, Am. J. Dis. Child. 63:748, 1942.
27. Rutishauser, E., Veyrat, R., and Rouiller, Ch.: La vascularisation de l'os pagétique, Presse méd. 31:654, 1954.
28. McIntosh, H. D., Gleason, W. L., Miller, D. E., and Bacos, S. M.: Circulatory dynamics in polyostotic fibrous dysplasia, J. Clin. Invest. 38:1023, 1959.

Congenital coronary arteriovenous fistula
Report of a case with an analysis of seventy-three reported cases

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The purpose of this paper is to report a case of congenital coronary arteriovenous fistula and to review the complete literature on the subject. An attempt is made to determine the frequency of association of this congenital anomaly with other congenital cardiovascular abnormalities. The results in all cases of operation are examined.

Case report

G. McB. is a 5-year-old white boy who was first seen on Dec. 6, 1960, for evaluation of a murmur in the chest. His parents stated that he had never been as active as other children, and they attributed this to ease of fatigue on exertion. There had been no cyanosis or dyspnea, and development in other respects had been normal. The murmur was noted first at 4 years of age when he was examined for an upper respiratory infection. Four older siblings are normal. A first cousin (maternal side), 31 years of age, has a patent ductus arteriosus with pulmonary blood pressure at systemic level.

The patient was a well-developed and well-nourished 5-year-old white boy with a distinct pallor to the skin. The blood pressure was 105 mm. Hg systolic and 60 mm. Hg diastolic in the upper extremity and 110 systolic and 75 diastolic in the lower extremity. The teeth were carious. There was no cyanosis or clubbing. The edge of the liver was palpable 3 cm. below the right costal margin in the mid-clavicular line. The veins in the neck were not distended, and all peripheral pulses were normal. The point of maximum cardiac impulse was in the fourth left intercostal space in the mid-clavicular line. The cardiac rhythm was regular. The second heart sound varied normally with respirations. A moderately loud, harsh, continuous murmur was localized over the third and fourth left intercostal spaces along the sternal border. The murmur was louder in systole than in diastole, and its intensity was reduced by the Valsalva maneuver. The remainder of the examination gave findings which were within normal limits.

Routine studies of blood and urine gave findings which were within normal limits. The electrocardiogram was normal. Roentgenograms of the chest (Fig. 1) disclosed a straight border of the left side of the heart with a narrow aortic pedicle, but was within normal limits. A phonocardiogram (Fig. 2) taken over the fourth left intercostal space at the sternal border showed a prominent, high-frequency, continuous murmur with the systolic component more intense than the diastolic. Cardiac catheterization (Table I) performed on Jan. 17, 1961, showed a small left-to-right shunt at the ventricular level with normal right ventricular pressure. Tracings of a retrograde aortogram (by way of the right brachial artery, No. 6 cardiac catheter passed to the level of the aortic valve) which was made on the same day showed a fistula between the left and right coronary arteries and the right ventricle (Fig. 3).

Because of the patient's minimal disability, no operative intervention is planned in the near future, and he will be followed and re-evaluated periodically.

Discussion

Seventy-three cases of congenital coronary arteriovenous fistula have been reported to date.[1-73] An attempt has been made to classify these fistulae according to their recipient chambers (Table II). Of the 73 cases, 65 can be so classified; in 8 of the

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Fig. 1. Posteroanterior x-ray film demonstrating the straight border of the left side of the heart and the narrow aortic pedicle.

73 cases the data were not sufficient for proper classification. In 58 of the 65 cases (89.2 per cent) the fistulae emptied into the right side of the heart (right atrium including the coronary sinus and its tributaries, right ventricle, or pulmonary artery), whereas in 6 of the 65 cases (9.2 per cent) the fistulae emptied into the left side of the heart (left atrium or left ventricle); in 1 of the 65 cases (1.5 per cent) the recipient chamber was a single ventricle.

The artery of origin was the right coronary artery in 30 cases, the left coronary artery in 18, and an extra coronary artery in 1; in 6 cases the artery was not specified. In 10 cases both coronary arteries participated in the fistula (Table III). It is apparent that fistulae involving the pulmonary artery and especially the right ventricle are more likely to receive blood from both coronary arteries than are those fistulae which empty into the right atrium. Likewise, they not infrequently empty into more than one chamber.

Associated congenital cardiovascular defects. Twenty-two[illegible] of the 65 patients with congenital coronary arteriovenous fistula had associated congenital cardiovascular defects. These are summarized and classified in Table IV. The frequency of this association (22 of 65 cases or 33.8 per cent) has not been emphasized previously. Surprisingly, these patients fall into six major groups. Most of the patients in the first 3 groups had multiple cardiovascular anomalies, whereas this was not so for the last three groups.

In Group I, 7 patients had coronary arteriovenous fistula, pulmonary valvular atresia, and patent ductus arteriosus. In each instance the fistula connected the coronary artery system with a ventricle (right ventricle in 6 cases and single ventricle in 1 case). There was probably no

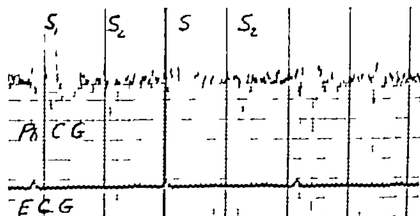


Fig. 2. Phonocardiogram taken over the fourth left intercostal space at the sternal border demonstrating a prominent high-frequency continuous murmur with the systolic component more intense than the diastolic. (Taken with a Sanborn Twin-Beam logarithmic phonocardiogram.)

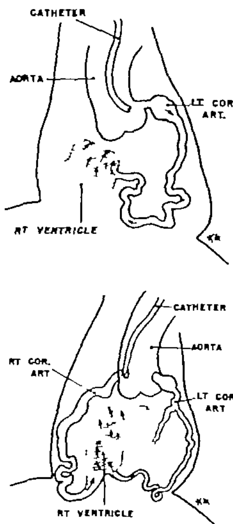


Fig. 3. Tracings of retrograde aortogram. *Top.* Anteroposterior view showing the dilated and tortuous left coronary artery. *Bottom.* Left anterior oblique view with catheter tip in the right coronary artery showing the dilated and tortuous vessel and dye entering the right ventricle.

flow of blood through these fistulae in ventricular systole, and in diastole the flow of blood was probably toward the ventricle.

In Group II 3 patients had coronary arteriovenous fistula pulmonary valvular atresia, and ventricular septal defect The fistulae in the first 2 cases of this group[4,21] emptied into the right ventricle and their function was probably similar to those in Group I In the third case[20] the fistula emptied into the pulmonary artery and was its only source of blood

In Group III 2 patients[22,23] had coronary arteriovenous fistula and aortic valvular atresia both died within 38 hours after birth and multiple cardiac defects were present. In both cases the fistula was between the coronary artery system and the left ventricle With obstruction of the left ventricular outflow tract the direction of flow of blood in the fistula in the case of Bellet and Gouley[22] was likely from the coronary artery system to the left ventricle in ventricular diastole but in the reverse direction in Blakeway's case.[23] In ventricular systole there was probably no flow of blood in these fistulae The obstruction of the ventricular outflow tract was probably an important factor in the development of these fistulae.

In Group IV 4 patients[1,21,23,24] had coronary arteriovenous fistula and patent ductus arteriosus in one,[22] pulmonary hypertension was a complication. When these 4 patients are added to the 8 in Groups I and II [6,10,15,4,20] there are 12 patients out of 65 which have these two anomalies associated. When the 2 patients who died before they were 3 weeks of age[8,10] are omitted there is a remainder of 10 patients of the 65 with the two anomalies associated.

In Group V 4 patients had coronary arteriovenous fistula and various defects of the blood vessels. The first[14] had an associated kinking of the aortic arch In the second[19] the fistula received one vessel from

Table I Data from cardiac catheterization

Site	Pressure (mm. Hg)	Saturation (%)
Superior vena cava		66 9
Right atrium		
High		68 8
Mid	2 (Mean)	72 0
Right ventricle		
Inflow	25/3	77 3
Outflow		77 9
Main pulmonary artery	20/5	78 2
Pulmonary artery wedged	4 (Mean)	
Left ventricle	104/7	
Aorta	104/66	94 9
Systemic flow		2 8 L./min.
Pulmonary flow		3 5 L./min.
Left-to-right shunt		0 7 L./min.
Pulmonary flow is 1.2 times systemic flow		

*Van Slyke method.

Table II *Congenital coronary arteriovenous fistulae classified according to the recipient chamber*

Recipient chamber	*Number*	*From right coronary artery*	*From left coronary artery*	*Mixed*	*Not specified*	*From extra coronary artery*
Right atrium	23	15	4	0	3	1
Right ventricle	25	10	6	6	3	0
Pulmonary artery†	10	4	3	3	0	0
Left atrium	3	0	3	0	0	0
Left ventricle	3	0	2	1	0	0
Single ventricle	1	1	0	0	0	0
Total	65	30	18	10	6	1

*Includes coronary sinus and tributaries.
†Includes one case[36] of anomalous left coronary artery functioning as an arteriovenous fistula.

Table III *Coronary arteriovenous fistulae arising from both coronary arteries*

Reference	*Recipient chamber*	*Supplying arteries*
No. 3	Right ventricle	Left coronary artery/right coronary artery
No. 5 (Case 1)	Right ventricle	Left coronary artery/right coronary artery†
No. 5 (Case 3)	Right ventricle	Right coronary artery‡
No. 6	Right ventricle	Right coronary artery/left coronary artery
No. 16	Right ventricle	Right coronary artery/left coronary artery
Present case	Right ventricle	Left coronary artery/right coronary artery
No. 13	Pulmonary artery	Right coronary artery/left coronary artery/pericardiophrenic artery
No. 17	Pulmonary artery	Right coronary artery/left coronary artery
No. 18	Pulmonary artery	Left coronary artery/right coronary artery
No. 15	Left ventricle	Left coronary artery/right coronary artery‖

*Fistula also emptied into the base of the pulmonary artery.
†Also right coronary artery–right ventricle fistula.
‡One coronary artery arose de novo from the anterior myocardium (septum) and passed to the left aorta.
‖Fistula also emptied into the left atrium.

the left subclavian artery and one vessel from the posterior aspect of the aortic arch in addition to its supply from the right coronary artery in the third[28] only one coronary artery (right) was present and the venous drainage of the heart was primarily into the pulmonary artery. The fourth[17] was a fetus of 22 weeks gestation in which three coronary arteries arose from the left posterior aortic sinus, and three from the right anterior aortic sinus.

Group VI contains 2 unrelated cases. One[23] patient had had a transient right hemiplegia at 2 years of age. The electrocardiogram of the second[24] showed probable pre-excitation (Wolff Parkinson White syndrome).

Results of operation Corrective operation has been attempted in 23 cases.[1,2,4,7,8,11,12,13,20,21,24] The results of operation are summarized in Table V. The sole postoperative death occurred in a 2½-year-old child[22] who had a left coronary artery–right atrium fistula and associated patent ductus arteriosus the pulmonary blood pressure was at systemic level. Both the ductus and the fistula were repaired but the child died suddenly on the day after the operation. The patient who was not improved by operation was a 56-year old woman[19] with a left coronary artery–right ventricle fistula and congestive heart failure. The pulmonary blood pressure was moderately elevated (70 mm. Hg systolic and 25 mm Hg diastolic) probably secondary to both the heart failure and the fistula.

Those patients who had a poor operative result or who developed major operative or postoperative complications were either

very young[illegible] (1 to 9 years of age) or beyond middle age[illegible] (53 and 56 years of age) whereas those patients who had a satisfactory and uncomplicated postoperative course ranged between 10 and 43 years of age.[illegible] Exceptions to this general observation disclosed an uncomplicated postoperative course in 4 patients aged 9 months,[1] 14 months,[1] 4 years,[illegible] and 6 years.[illegible] Nevertheless the pattern seems clear that the best age group for operative repair of these fistulae is that between 10 and 45 years. Operative repair in patients younger than 10 years or older than 45 years probably carries with it an increased chance of morbidity and mortality. The presence of an additional preoperative cardiovascular defect such as a patent ductus arteriosus or a fistula supplied by more than one artery or emptying into more than one chamber is not in itself a contraindication to operation and probably does not increase the surgical risk. Rather the complications attendant on such defects, such as congestive heart failure or pulmonary hypertension seem to raise the risk.

Table IV. Associated congenital cardiovascular defects

Total number with associated congenital cardiovascular defects	22
Group I—Pulmonary valvular atresia and patent ductus arteriosus[illegible]	7
Group II—Pulmonary valvular atresia and ventricular septal defect[illegible]	3
Group III—Aortic valvular atresia[illegible]	2
Group IV—Patent ductus arteriosus[illegible]	4
Group V—Other blood vessel defects[illegible]	4
Group VI—Other congenital cardiovascular defects[illegible]	2

Table V. Summary of data from operations

Total number of operations	23
Death[illegible]	1
Result not stated[illegible]	1
Recovery but not improved*[illegible]	1
Recovery and improved*[illegible]	20
Operative and postoperative complications	7
Minor (transient S-T and T-wave changes in ECG)[illegible]	3
Major	
Developed extreme bradycardia as pleura was entered[1]	1
Developed pericarditis postoperatively	1
Recovery after a stormy postoperative course[illegible]	1
Developed myocardial infarction postoperatively[illegible]	1
Preoperative associated cardiovascular complications	17
Patent ductus arteriosus[illegible]	2
Congestive heart failure[illegible]	3
Dyspnea and/or cardiac enlargement[illegible]	9
Pulmonary blood pressure at systemic level[illegible]	1
Fistula supplied by more than one artery and/or emptied into more than one chamber[illegible]	2
Preoperatively no associated cardiovascular complications; asymptomatic[illegible]	4
Preoperative status not stated[illegible]	6

*"Improved" defined as the disappearance of symptoms and/or murmur.

Summary

A case of left and right coronary artery—right ventricle fistula is presented. The literature is reviewed and brought up to date on this subject. These fistulae are classified according to the heart chamber into which they empty. They usually originate from one coronary artery but not infrequently they originate from both. The latter situation is most likely to occur when the fistula empties into either the right ventricle or the pulmonary artery.

Of the 65 patients studied 22 had congenital coronary arteriovenous fistula associated with some other congenital cardiovascular defect. These were classified into six groups. Particularly striking was the association of coronary arteriovenous fistula and pulmonary valvular atresia (10 cases); patent ductus arteriosus was an associated lesion in 7 of these and ventricular septal defect in 3. Patent ductus arteriosus was associated with congenital coronary arteriovenous fistula in 10 of the 65 cases.

Of 23 patients who have been operated upon and reported upon to date 1 patient died and 1 was not improved. 4 suffered major operative or postoperative complications. Yet 20 of the 23 recovered and were improved.

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cardiac catheterization to Dr. B. B. Gay Jr. who made the retrograde aortogram, and to Dr. J. W. Hurst for helpful suggestions in the preparation of this manuscript.

REFERENCES

1. Gasul, B. M., Arcilla, R. A., Fell, E. H., Lynfield, J., Bicoff, J. P., and Luan, L. L.: Congenital coronary arteriovenous fistula, Pediatrics 25:531, 1960.
2. Aitken, G. J.: Coronary arteriovenous fistula, Scottish M. J. 4:27, 1959.
3. Zuhdi, N., Kraft, D., Carey, J., and Greer, A.: Coronary arteriovenous-like communications, A.M.A. Arch. Surg. 80:178, 1960.
4. Amplatz, K., Aguirre, J., and Lillehei, C. W.: Coronary arteriovenous fistula into main pulmonary artery, J.A.M.A. 172:1384, 1960.
5. Muir, C. S.: Coronary arterio-cameral fistula, Brit. Heart J. 22:374, 1960.
6. Guldiel, C., and Becu, L.: Case reports cardio-aortic fistula through anomalous coronary arteries, Brit. Heart J. 22:729, 1960.
7. McIntosh, H. D., Sleeper, J. C., Thompson, H. K., Jr., Sealy, W. C., and Young, W. G., Jr.: Preoperative evaluation of a continuous murmur in the chest, A.M.A. Arch. Surg. 82:74, 1961.
8. Engle, M. A., and Ito, T.: The post pericardiotomy syndrome, Am. J. Cardiol. 7:73, 1961.
9. Wedell, H. G., and Teloh, H. A.: Congenital communication between the right coronary artery and the right atrium, Quart. Bull. Northwestern Univ. M. School 33:283, 1959.
10. Currarino, G., Silverman, F. N., and Landing, B. H.: Abnormal congenital fistulous communications of the coronary arteries, Am. J. Roentgenol. 82:392, 1959.
11. Wood, P.: Diseases of the heart and circulation, ed. 2, Philadelphia, 1956, J. B. Lippincott Company, p. 912.
12. Craig, J. M.: Congenital endocardial sclerosis, Bull. Internat. A. M. Mus. 30:15, 1949.
13. Ernst, C. B., Klassen, K. P., and Ryan, J. M.: Vascular malformation overlying the pulmonary artery simulating a patent ductus arteriosus, Circulation 23:759, 1961.
14. Portsmann, W., and Gessler, W.: Über die arteriovenösen Fisteln der Koronararterien, Fortschr. Röntgenstrahl. 93:143, 1960.
15. Bellet, S., and Gouley, B. A.: Congenital heart disease with multiple cardiac anomalies: report of a case showing aortic atresia, fibrous scar in myocardium and embryonal sinusoidal remains, Am. J. M. Sc. 183:458, 1932.
16. Williams, R. R., Kent, G. B., and Edwards, J. E.: Anomalous cardiac blood vessel communicating with the right ventricle, A.M.A. Arch. Path. 52:480, 1951.
17. Scott, D. H.: Aneurysm of the coronary arteries, Am. Heart J. 36:403, 1948.
18. Bayliss, J. H., and Campbell, M.: An unusual cause for a continuous murmur, Guy's Hosp. Rep. 101:174, 1952.
19. Brooks, H. St. J.: Two cases of an abnormal coronary artery of the heart arising from the pulmonary artery: with some remarks upon the effect of this anomaly in producing cirsoid dilatation of the vessels, J. Anat. 20:26, 1886.
20. Abbott, M. E.: Anomalies of the coronary arteries, *in* McCrae, O. W., editor: Osler's modern medicine, Philadelphia, 1927, Lea & Febiger, pp. 794-796.
21. Sondergaard, T.: *In* Lam, Conrad R., editor: Henry Ford Hospital International Symposium on Cardiovascular Surgery, Philadelphia, 1955, W. B. Saunders Company, pp. 490-492.
22. Bosher, L. H., Jr., Sverre, V., McCue, C. M., and Belter, L. F.: Congenital coronary arteriovenous fistula associated with large patent ductus, Circulation 20:254, 1959.
23. Wilson, J. G., and Grant, R. T.: A case of congenital malformation of the heart in an infant, associated with partial heart block, Heart 12:295, 1926.
24. Alexander, W. S., and Green, H. C.: Coronary blood vessel arising from cardiac ventricle: report of a case showing other cardiac anomalies, A.M.A. Arch. Path. 53:187, 1952.
25. Allanby, K. D., et al.: Pulmonary atresia and collateral circulation to the lungs, Guy's Hosp. Rep. 99:110, 1950.
26. Brown, R. C., and Burnett, J. D.: Anomalous channel between aorta and right ventricle, Pediatrics 3:597, 1949.
27. Essenberg, J. M.: An anomalous left coronary artery in a human fetus: its passage through the left atrium and possible discharge into the right atrium, Anat. Rec. 106:709, 1950.
28. Paul, O., et al.: Coronary arteriovenous fistula: case report, Am. Heart J. 37:441, 1949.
29. Edwards, J. E., Gladding, T. C., and Weir, A. B.: Congenital communication between the right coronary artery and the right atrium, J. Thoracic Surg. 35:662, 1958.
30. Blakeway, H.: A hitherto undescribed malformation of the heart, J. Anat. & Physiol. 52:354, 1918.
31. Bjorck, G., and Crafoord, G.: Arteriovenous aneurysm on pulmonary artery simulating patent ductus arteriosus botalli, Thorax 2:65, 1947.
32. Sanger, P. W., Taylor, F. H., and Robicsek, F.: The diagnosis and treatment of coronary arteriovenous fistula, Surgery 45:344, 1959.
33. Neill, C., and Mounsey, P.: Auscultation in patent ductus arteriosus with a description of two fistulae simulating patent ductus, Brit. Heart J. 20:61, 1958.
34. Johnson, J.: Cited by Davis, C., et al.: Anomalous coronary artery simulating patent ductus arteriosus, J.A.M.A. 160:1047, 1956.
35. Swan, H., et al.: Surgical obliteration of a coronary artery fistula to right ventricle, A.M.A. Arch. Surg. 79:820, 1959.
36. Moore, H. E.: Congenital cirsoid aneurysm of coronary artery with associated arterio-atrial fistula treated by operation: a case report, Ann. Surg. 144:215, 1956.
37. Kittle, C. F.: *In* discussion of Gasul, B. M., et al.: Congenital coronary arteriovenous aneurysm, A.M.A. Arch. Surg. 78:201, 1958.
38. Morrow, A. G.: Cited by Edwards, et al.[29]
39. Diehl, A.: Personal communication to Gasul.

Congenital aneurysm of the sinus of Valsalva
Anatomy and classification

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After the first published case of ruptured congenital aneurysm of the sinus of Valsalva by Thurnam[1] in 1840, only 18 similar cases were reported in the following 100 years. In the next decade, however, 19 cases were reported and 51 more in the succeeding 10 years, showing a sharp rise in the incidence of this abnormality. This increased incidence is due to the great advance in the methods of diagnosing heart diseases and also to the emphasis upon early diagnosis since the recent striking progress in open-heart operation has made possible surgical correction of congenital aneurysms of the sinus of Valsalva.[2,3] Of the 12 cases of this malformation which we have encountered, operation was performed in 6.

In general, several morphologically different types that differ in symptomatology, progress of the lesion, and prognosis are included in the category of congenital aneurysm of the sinus of Valsalva. A clear understanding of the different types, therefore, is essential for the clinician. Inasmuch as no serious attention to the various types and no attempts to classify them properly have been made previously, it is our purpose in this paper to attempt a morphologic classification of the various types, based on our series of cases and those found in the literature.

Anatomic considerations

The sinus of Valsalva is defined as the hollow space enclosed by the three aortic cusps and the opposite aortic wall at the root of the aorta. The aortic wall in this area bulges slightly and three dilatations are normally found at the commencement of the aorta. The anatomic term *sinus of Valsalva* applies only to this dilated area, which corresponds to area *V* in Fig. 1. Strictly speaking, however, an aneurysm which originates from only this area is rarely found; most of them extend over into the areas *B* and *C*, so that the former definition would be more appropriate for clinical use.

The sinuses of Valsalva have each been given the name of their corresponding aortic cusp, but much confusion has resulted from the fact that two different systems of nomenclature of the aortic cusps have been used by previous investigators. By using the B.N.A. and P.N.A. system, in which the ventricular septum is taken as the mid-plane to divide the heart into right and left, and also the J.N.A. system, in which the position of the heart in the thorax determines the right or left direction, the same sinus was referred to by completely different names by different investigators. In this respect, due care must be taken when reading the literature.

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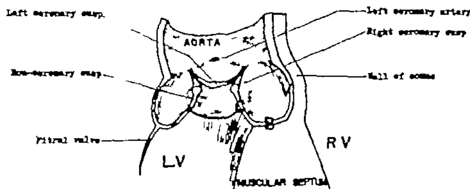


Fig 1 Longitudinal section of the root of aorta through nodules Arantii of the right coronary cusp to show the detail of the right coronary sinus. RV Right ventricle LV Left ventricle V Sinus of Valsalva in the strict meaning B Fixed part of the right coronary cusp C Free part of the right coronary cusp.

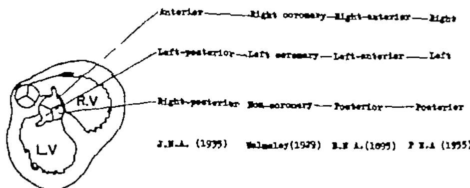


Fig 2 Diagram to show the interrelationship of three systems of naming the semilunar valves and their related aortic sinuses. RV Right ventricle. LV Left ventricle

The individual variation in the degree of rotation of the great vessels and consequently the considerable differences in the position of the sinuses of Valsalva were pointed out by Walmsley[8] in 1929 He proposed a method of nomenclature whereby the coronary ostium is taken to determine the terminology since this would eliminate the variable factors. That is the sinus of Valsalva into which the right coronary ostium opens would be called the right coronary sinus that into which the left coronary sinus opens the left coronary sinus and the sinus that had no communication with the coronary arteries, the non coronary sinus. Fig 2 is a diagram which shows the interrelation of the three systems of terminology The widely accepted and most rational method of Walmsley has been used in this report.

Since the sinus of Valsalva is located in the central portion of the heart near to the right and left atria and ventricles the cardiac conduction system and the coronary and pulmonary arteries even a small aneurysm which originated in this area would compress these vital structures or rupture and produce an aortico-cardiac fistula with subsequent manifestation of numerous and varied symptoms. A clear understanding of the exact topography of this area would be of immense value to the clinician but, unfortunately anatomic textbooks or articles dealing with this part of the heart in detail have yet to be published The only referable sources are those of Ostrum[10] Edwards,[11] and Gross[12] but they too give only simple descriptions or narrow the description to limited areas, which makes it difficult to grasp the re

lationship of the aortic sinuses to the other structures of the heart.

To throw light on this point in a dog's heart, sagittal sections radiating from the aortic ostium were made as shown in Fig 3 and the relationship of the sinus of Valsalva to the surrounding structures of the heart was studied. The relationships in the dog's heart are generally the same as those in the human heart. Fig 4 shows the left sagittal section of the heart through the left part of the right coronary sinus and the left part of the noncoronary sinus. The left part of the right coronary sinus is adjacent to the conus of the right ventricle. Aneurysms frequently originate in this area and protrude just below the commissure of the right and left pulmonary cusps (Type I) The direction in which the aneurysm projects is shown by the arrow The left part of the noncoronary sinus does not touch any other part of the heart but is covered by the pericardium and faces the pericardial cavity Fig 5 shows the right sagittal section of the heart through the central part of the right coronary sinus and the posterior part of the left coronary sinus. The central part of the right coronary sinus is next to the crista supraventricularis of the right ventricle. An aneurysm which develops in this area although quite rare, burrows through the crista supraventricularis and protrudes into the outflow tract of the right ventricle (Type II)[3,11,26] The posterior part of the left coronary sinus does not touch any other part of the heart. It is covered by the pericardium and faces the pericardial cavity Fig 6 shows the right posterior sagittal section of the heart through the posterior part of the right coronary sinus and the central part of the left coronary sinus. The posterior part of the right coronary sinus is separated from the right atrium and ventricle by the membranous septum and is also adjacent to the bifurcation of the vital conduction system This area is the second most frequent site of formation of congenital aneurysms. Aneurysms which originate in this area protrude mostly into the right atrium (Type IIIa) A few are found projecting into the right ventricle (Type IIIv) and in rare instances, into both the right atrium and right ventricle (Type IIIa+v) The central part of the left coronary sinus is covered by the pericardium and faces the pericardial cavity Fig 7 shows the right anterior sagittal section through the right part of the noncoronary sinus and the right part of the left coronary sinus. The right part of the noncoronary sinus touches the right atrium Aneurysms in this area protrude into the right atrium (Type IV) Because this part of the sinus of Valsalva is near the atrioventricular node and the bundle of His aneurysms which originate here may cause arrhythmias. The right part of the left coronary sinus is near the pulmonary sinus. The central and right parts of the left coronary sinus are situated exteriorly and the base of the sinus is adherent to the muscle in the anterior wall of the left ventricle The aortic wall of the sinus of Valsalva is covered by one layer of the pericardium and bulges out into the pericardial cavity

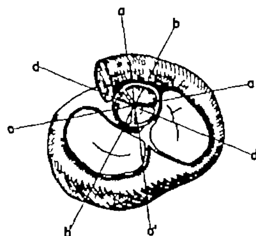


Fig 3 The heart viewed from above to show the anatomic relationship between the aortic sinuses and the atria. The radiating lines show the sections which were made to disclose the topography of the aortic root. The sections are shown in Figs. 4 5 6, and 7

Mode of development

When the anatomic relationship just described is taken into consideration it would be conceivable for aneurysms to develop in every sinus but, actually over 95 per cent of the aneurysms originate in the right coronary sinus and right part of the noncoronary sinus, projecting into the right ventricle or atrium (see Table II)

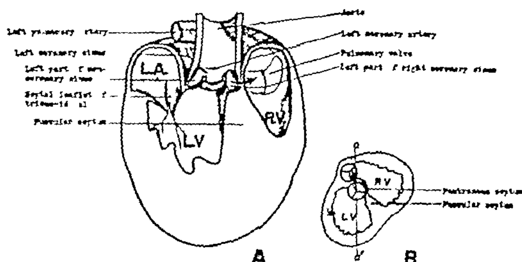


Fig. 4. *A*, Semischematic drawing of the left sagittal section; the heart was cut longitudinally in the direction represented by *a-a*. *B*, Diagram to show the relationship of the aortic sinuses to the ventricles. The aortic and pulmonary ostia are projected onto a schematized cross section of the underlying ventricles.

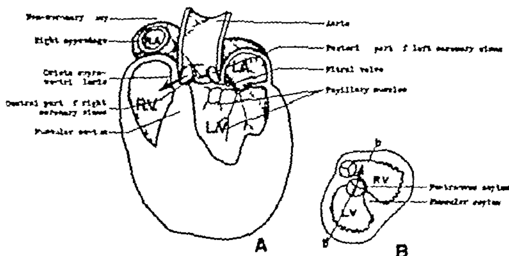


Fig. 5. *A*, Semischematic drawing of the right posterior section; the heart was cut longitudinally in the direction of *b-b*. *B*, Diagram to show the relationship of the aortic sinuses to the ventricles. Pulmonary and aortic ostia are projected onto a schematized cross section of the underlying ventricles.

aneurysm of the sinus of Valsalva and finding all to have originated from the right coronary sinus. M. E. Abbott[13] in 1919 advanced the opinion that congenital aneurysms of the sinus of Valsalva are the result of dilatation caused by the high blood pressure acting on a weak point in the aortic wall due to inadequate fusion of the bulbar septum. Jones and Langley[14] examined 48 cases in 1949 and supported Abbott's observation. Only the right coronary and noncoronary sinuses are related to the bulbar septum, and when the right and left bulbar ridges do not fuse, a tissue defect occurs which results in the formation of an aortico-cardiac fistula. Even if fusion occurs but is inadequate, a point of weakness persists which develops into an aneurysm from the pressure of the blood. However, careful perusal of the literature

discloses that aneurysms of the left coronary sinus are not completely absent. Kurt Walcher[17] in 1921, A. R. Higgins[18] in 1934, R. H. Micks,[19] in 1940, and T. K. Raman[20] in 1949 have reported one case each. In 1951 Venning[21] stated that the cause of aneurysms of the sinus of Valsalva was the local defect of elastic tissue at the base of the aorta. Edwards[22] in 1956 after detailed histologic examination of the base of the aorta stated that the fundamental cause of aneurysms of this area was the separation of the aortic media and the annulus fibrosus of the aortic valve. These two concepts would advantageously explain the production of aneurysms of the left coronary sinus but in the first place, it should be remembered

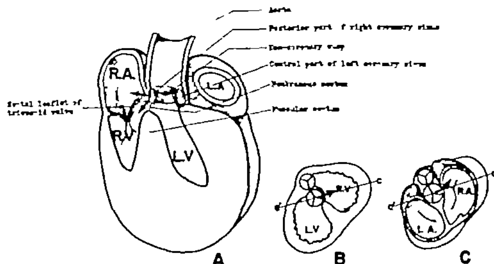


Fig 6 *A* Semischematic drawing of the dorsal section the heart was cut longitudinally in the direction of *c-c*. *B* Diagram to show the relationship of the aortic sinuses to the ventricles. Pulmonary and aortic ostia are projected onto a schematized cross section of the underlying ventricles. *C* The heart viewed from above, to show the relationship between the aortic sinuses and atria.

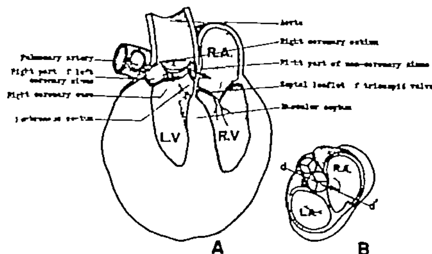


Fig 7 *A* Semischematic drawing of the right ventral section the heart was cut longitudinally in the direction of *d-d'*. *B* The heart viewed from above, to show the relationship between the aortic sinuses and [illegible]

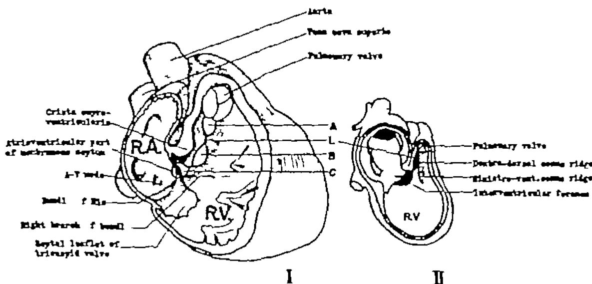


Fig. 8. I. Adult heart viewed from right. A part of the right atrium and ventricle was removed to visualize the inside of the heart. Black area represents the tissue which corresponds to the dextrodorsal truncus ridge. Dotted area represents the tissue which corresponds to the sinistroventral truncus ridge. II. Heart of embryo.

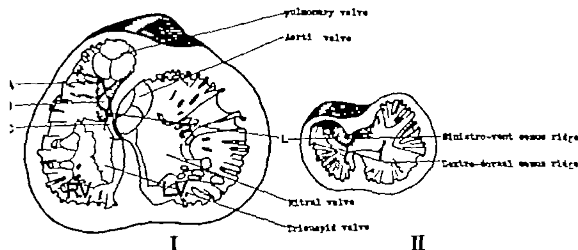


Fig. 9. I. Base of adult heart viewed from apex. A part of the ventricle was removed to visualize the inside of the heart. Black area represents the tissue which corresponds to the dextrodorsal truncus ridge. Dotted area represents the tissue which corresponds to the sinistroventral truncus ridge. II. Heart of embryo.

that aneurysms of the left coronary sinus are exceedingly rare. Of the 4 cases which appear in the literature, the evidence which points to their congenital origin is not altogether convincing; in fact, some cases appear to have a syphilitic origin. In either event, these 4 cases comprise only a very small number of the 90 cases reported and thus are not sufficient evidence against Abbott's or Jones and Langley's theory.

Venning and Edward observed only the histologic picture of pre-existing pathologic states, and no embryologic consideration in regard to the presence of weak tissue or the separation of the aortic media and annulus fibrosus of the aortic valve was given. Jones and Langley's explanation is clear and well conceived, but because of the simplified diagrammatic representation tends to leave many points unanswered.

By comparing the mature heart and the embryonic heart as shown in *I* and *II* of Figs. 8 and 9 and by plotting the areas in the heart which correspond to the sinistroventral conus ridge and dextrodorsal conus ridge of the embryonic heart one can draw a line which corresponds to the fused line of the right and left conus ridges at the outflow tract of the mature heart. Starting from the membranous septum this line crosses over the crista supraventricularis and passes through the commissure of the right and left pulmonary cusps (Fig 8,*L*) This imaginary line, viewed from the left ventricle, starts from the membranous septum curves along the base of the right coronary cusp passes through the commissure of the right and left coronary cusps, and rises along the aorta (Fig 10,*L*) Although this line is imaginary the author has frequently observed a linear translucent strip of thin tissue which corresponds to this imaginary line in the hearts of patients who died of other diseases. When both sides of the conus ridges do not fuse at the area marked *A* in Figs. 8 9 and 10 a high ventricular septal defect is formed Of the cases of ventricular septal defect in which operation was performed 10.3 per cent were of this type. Viewed from the left ventricle area *A* corresponds to the left part of the right coronary cusp just below the attached line of the cusp. When this attached line is situated lower area *A* will be included in the sinus of Valsalva and an aortico-cardiac fistula will develop. Such a case was reported by Jacobi[20] Inadequate fusion of the right and left conus ridges with persistence of weak tissue at this portion will result in gradual dilatation of this area into the outflow tract of the right ventricle due to the high pressure of the blood with eventual formation of an aneurysm. This is the Type I aneurysm of the sinus of Valsalva. When area *A* is transversed by the attached line of the right coronary cusp and a weak point above and a tissue defect below the attached line exist, the right coronary cusp and wall of the sinus of Valsalva, having lost their support will sink into the defect from the action of the blood pressure and thus develop into a high ventricular septal defect with aortic insufficiency Furthermore, under continued pressure, the weakened area of the sinus of Valsalva will balloon out through the ventricular septal defect into the outflow tract of the right ventricle. This is the Type Ivsd aneurysm of the sinus of Valsalva. The process in the development of this type is diagrammatically described in Fig 11 the upper figure shows the section and the lower figure,

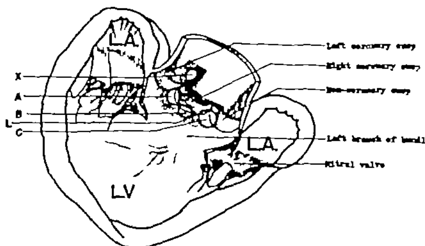


Fig *10* Opened heart viewed from left ventricular side Black area represents the tissue which corresponds to the dextrodorsal truncus ridge. Dotted area represents the tissue which corresponds to the sinistroventral truncus ridge

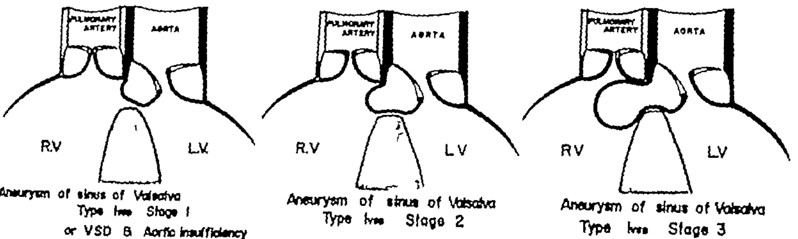
the outflow tract visualized at operation When the right and left truncus ridges do not fuse at area *B* a ventricular septal defect is formed at the crista supraventricularis but these cases are rare. When inadequate fusion takes place at this area, and an area of fragility remains the pressure of the left ventricle causes pouch-like projection of this area into the right ventricle. This malformation has been given the name of *congenital interventricular septal aneurysm* Rupture occurs when dilatation of the aneurysm reaches a certain extent and a shunt between the ventricles is produced. Such cases have not been reported in the medical literature but we have performed an operation in 2 such cases.[21]

Viewed from the left ventricle area *B* is just below the attached line of the right coronary cusp. If the line of attachment descends area *B* becomes included in the right coronary sinus. It is rare however in this instance for an aneurysm to form even when a weak point in the tissue exists. Four cases are reported[4, 11] in which no aneurysms were found in spite of the existence of a weak area in the sinus wall and only one case[11] of an aneurysm which originated from this area has been reported in the literature (Type II) A patient on whom we recently operated (Case 12) was found to have an aneurysm which originated from this area. When the line of attachment of the right coronary cusp transverses area *B* and an area of weak tissue above and a tissue defect below the line of attachment exist an aneurysm of the sinus of Valsalva and a ventricular septal defect form side by side at the crista supraventricularis (Type IIvsd) On the basis of the illustration given in Kirklin's report [9] it appears that his case is of this type

Area *C* or the membranous septum is constituted of endocardial cushion tissue derived from the dextrodorsal and sinistroventral conus ridges, the right tubercle of the dorsal and ventral atrioventricular canal cushion and the crest of the muscular interventricular septum. This portion is bordered by the septal leaflet of the tricuspid valve and is in close relation to both the right atrium and right ventricle (Fig. 8) Viewed from the left ventricle it is near to the posterior part of the right coronary sinus and the right part of the noncoronary sinus. Thus, its topographical relation is quite complicated (Fig. 10) Nonfusion of the endocardial tissue at this portion results in membranous septal defect. Incomplete union and persistence of unusually weak tissue results in a protrusion of this area into the right ventricle due to the pressure in the left ventricle with formation of an aneurysm of the membranous septum. When the posterior part of the right coronary sinus extends to the weak portion of *B* an aneurysm of the sinus of Valsalva develops because of the action of the high aortic pressure (Type III) As seen in Fig 6 this area involves both the right atrium and right ventricle and an aneurysm which originates in this area will point sometimes into the right ventricle (Type IIIv) and sometimes into the right atrium (Type IIIa) In rare instances it may protrude into both the right atrium and right ventricle.[12-14] If a tissue defect exists in this area, an aortico-cardiac fistula which communicates with both the right ventricle and right atrium is produced. This type of malformation is believed to have existed in the heart of the 27-day old infant reported on by Livingston.[25]

When the right part of the noncoronary sinus extends to the weak area of *B* aneurysms which originate in this area penetrate the tissue in the direction shown by the arrow in Fig 7 and project into the right atrium (Type IV) One case each of membranous septal defect associated with Type IIIv (Type IIIvsd)[26] and membranous septal defect associated with Type IV aneurysm of the sinus of Valsalva (Type IVvsd)[11] have been reported

Aortic septal defect results when fusion of the right and left truncus ridges does not take place at area Y (Fig 10) When a defect between areas *A* and *Y* forms the pulmonary sinus, sinus of Valsalva and a high ventricular septal defect are included in this defective area, and the result is the formation of an extremely complicated shunt The case reported by E. Richards[27] of combined high ventricular septal defect and sinus of Valsalva-pulmonary aortic fistula belongs to this type of malformation. A recently observed case of rupture of a Type Ivsd aneurysm associated with a



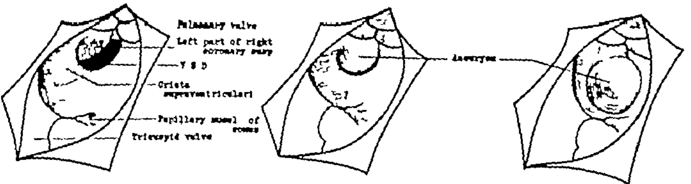


Fig. 11 Growing process of aneurysm of sinus of Valsalva of Type Ivm

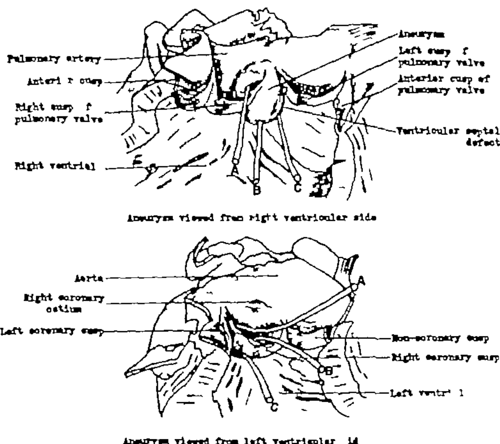


Fig. 1. Complication of aneurysm of sinus of Valsalva of Type IVb and aortico-pulmonary fistula. Case 8. 42-year-old woman. Sound *A* passes through aneurysm from pulmonary artery to right coronary sinus. Sound *B* passes through aneurysm from right ventricle to right coronary sinus. Sound *C* passes through ventricular septal defect from right ventricle to left ventricle.

aortico pulmonary arterial fistula is believed to have been due to malunion of the right and left truncus ridges at this point (Fig. 12).

This rather arbitrary speculation has been presented here not to advance an embryologic theory on the development of these malformations but to try to condense and unify the theories of development of aortic septal defect, aneurysm of the sinus of Valsalva, aortico-cardiac fistula, ventricular septal defect, congenital interventricular septal aneurysm, and aneurysm of the membranous septum, in a form readily understood by clinicians.

Types of aneurysms of the sinus of Valsalva

Since the term *aneurysm of the sinus of Valsalva* in its morphologic sense embraces any aneurysmal dilatation which originates in the sinus of Valsalva, its application is quite wide. Included in this entity are those aneurysms which result from syphilitic lesions[11-32, 44] as well as those from tuberculosis.[31] Aneurysms which develop subsequent to bacterial endocarditis[33-37, 42, 46] are also included. Pseudoaneurysms that develop after organization of hematomas which communicate with the sinus of Valsalva are often misdiagnosed as aneurysms of the sinus of Valsalva because of the close resemblance.[38-40, 48] Although those which are due obviously to acquired diseases, such as syphilis and tuberculosis, are differentiated and excluded in this consideration of congenital aneurysms of the sinus of Valsalva, it is quite difficult to decide, even histologically, when bacterial endocarditis was clinically demonstrated or found at autopsy, whether the lesion occurred secondary to a congenital aneu

rysm of the sinus of Valsalva or whether it was the causal factor in the production of the aneurysm.

However congenital aneurysms of the sinus of Valsalva follow a definite pattern in the site of origin and direction of dilatation ordained by the developmental process in the embryonic period whereas acquired aneurysms due to inflammatory processes which involve tissues indiscriminately protrude or rupture in directions that are inconceivable from the standpoint of embryology. Thus, it is possible to differentiate between the two in most instances. For instance, K. Hart's case of a noncoronary sinus aneurysm which was adherent to and projected into the left atrium is strongly suspected to be of the acquired type.[illegible] Several cases of pseudoaneurysm which have been reported appear to have developed after intramural rupture of a congenital aneurysm and subsequent formation of a hematoma and organization. K. Hart's case of a right coronary sinus aneurysm which ruptured into the left ventricle,[41] and similar cases reported by R. Warthen[illegible] and J. E. Edwards[11] are suspected as having been formed through this process. The case reported by Tanaka[illegible] of a congenital right coronary sinus aneurysm which ruptured into the left ventricle appears to be different from the 3 cases mentioned above although accurate evaluation is impossible since the morphologic description was not given in detail. The aneurysm in this case originated principally from the area which corresponds to *C* in Fig. 1 but the chief lesion appeared to be malformation of the aortic valve. In either case positive evidence as to its congenital nature seemed to be lacking. The fact that it is almost impossible to decide whether these aneurysms are congenital or acquired however is of little importance. What is more important is to have a clear understanding of the pathoanatomic relationship and to be

Table I. Growing process of aneurysm of the sinus of Valsalva

Congenital cause	*Congenital lesion in aortic sinus*	*Acquired cause*		*Acquired lesion aortic sinus*	
		Tuberculosis →	Blood pressure →	Irregular aneurysm	Acquired aneurysm
		Syphilis →	Blood pressure →	Irregular aneurysm	
		Bacterial endocarditis →	Blood pressure →	Irregular aneurysm	
Incomplete fusion of the conus ridges →	Localized fragile tissue →	Bacterial endocarditis →	Blood pressure →	Irregular diverticular aneurysm	Congenital aneurysm in narrow meaning
Incomplete fusion of the conus ridges →	Localized fragile tissue →	→	Blood pressure →	Diverticular aneurysm	
Incomplete fusion of the conus ridges →	Localized fragile tissue →	Rupture into muscular layer →	Hematoma →	Pseudo-aneurysm	Congenital aneurysm
Medionecrosis as a part of Marfan syndrome →	Diffuse fragile tissue →	→	Blood pressure →	Diffuse aneurysm	
Underdevelopment of elastic tissue →	Diffuse fragile tissue →	→	Blood pressure →	Diffuse aneurysm	
Unknown →	Unknown →	Hypertension due to coarctation of aorta →	→	Aneurysm	

aware that this type of lesion does occur although rarely

Walcher[17] and Micks[18] have each reported a case of diffuse dilatation of the sinus of Valsalva which appears to have resulted from congenital weakness of the elastic fibers of the aorta. Dilatation occurs as the sinus of Valsalva is subjected to the strongest action of the blood pressure. As illustrated in Figs. 6 and 7 the sinus which offers the least resistance is the left coronary sinus, since it is situated on the exterior surface of the heart. In this instance the greatest dilatation is seen in the left coronary sinus which presses aside the pulmonary artery and left auricle of the

Table II Classification of congenital aneurysm of sinus of Valsalva

Sinus of Valsalva from which the aneurysm arises		Right coronary sinus (R.C.S.)	
Encroached part of the sinus of Valsalva		Left part of the R.C.S. Type I	Central part of the R.C.S. Type II
Direction of protrusion and cardiac chambers into which the aneurysm protrudes		Into the conus of the right ventricle just beneath the commissure of the right and left pulmonary valves	Into the right ventricle, penetrating the crista supraventricularis
Without ventricular septal defect		I Thurnam, 1840 33 M Jones and Langley 1944 41 M Sakakibara 1954 Case 1—31 M Sakakibara, 1954 Case 2—33 F Sakakibara 1959 Case 6—19 M	II Edwards, 1957 75 M Sakakibara, 1960 Case 12—32, M
With ventricular septal defect	V.S.D of the pars membranaceus	Winchell, 1956 37 M	
	V.S.D at the crista supraventricularis		IIvsd Kirklin, 1958: 26 F
	V.S.D just beneath the pulmonary valve	Ivsd Beck, 1841 31 M Rickards, 1881 30 M Hart 1905 23 M Burchell, 1950 34 M Lin, 1954 13, M Kimoto, 1955 Case 1—23 M Brofman, 1956 26, M Kimoto, 1956 Case 2—19 M Kimoto, 1956: Case 3—21 M Sakakibara, 1957: Case 3—32, F Sakakibara 1957 Case 4—32 M Oguro, 1957: 37 M Kimoto, 1957: Case 4—10, F Sakakibara, 1958: Case 5—36, F Kimoto, 1958: Case 4—24 M Sakakibara, 1959: Case 7—10 M Sakakibara, 1960: Case 11—5 M	

*Cases of bicuspid aortic valves. See text.

heart and bulges out on the anterior surface of the heart. In Macleod's case this aneurysm ruptured into the pericardial cavity and death occurred due to tamponade. Raman[34] reported a case of aneurysms which originated from both the right and left coronary sinuses. The aneurysm of the right coronary sinus appeared to be similar to that reported by Warthen[42] but the one from the left coronary sinus was a hitherto undescribed type. This small aneurysm which was of about 5 c.c. in capacity originated from the base of the left coronary sinus and penetrated into the muscles of the left anterior ventricular wall. In Marfan's syndrome the aortic media

		Noncoronary sinus (N.C.S.)
Posterior part of the R.C.S. *Type III*		*Right part of the N.C.S.* *Type IV*
Into the right ventricle, just beneath the septal leaflet of the tricuspid valve penetrating the membranous septum	*Into the atrium near the commissure of the septal and anterior leaflets of the tricuspid valve*	*Into the right atrium, near the septal leaflet of the tricuspid valve*
IIIv Lillehei, 1959 Case 1—11 M Lillehei, 1959 Case 2—19 F Bigelow 1957 39 M	IIIa Krzywicki, 1888 20 F Abbott, 1919 36, M Wright, 1937 27 M Hauser 1940 49 M Hirschboeck, 1942 20, M Macleod, 1944 54, M Venning 1951 Case 1—56 M Hufeldt, 1956 24 F Lillehei, 1956 Case 3—37 M Morrow 1957 27 M Russell, 1960 Case 2—56 F	IV Gohring, 1920 26, M Duras, 1942 49 M Kawasaki, 1946 22, M Herson, 1946 31 F Maynard, 1948 23 M Kirklin[38] Oram, 1955 Case 2—67 M Edwards, 1956 42 F Winfield, 1959 24 M Peltzer 1959 38, M Sakakibara, 1960 Case 10—28 F
IIIv VSD White, 1892 15 M	IIIa VSD	IV VSD Edwards, 1957 28, M

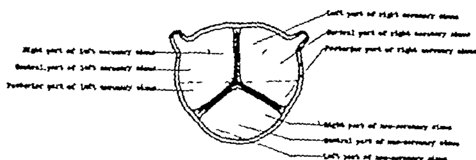


Fig. 13. Cross section of sinuses of Valsalva.

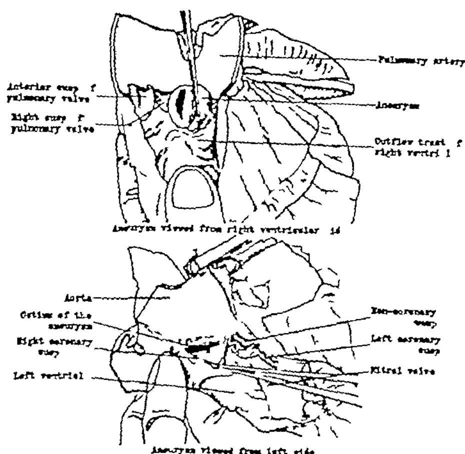


Fig. 14. Ruptured aneurysm of sinus of Valsalva of Type I. Case 1. 31-year-old man.

at the base of the aorta sometimes degenerates with subsequent formation of an aneurysm due to the high aortic pressure.[44-47] In contrast to the cyst-like formation of congenital aneurysms of the sinus of Valsalva, diffuse dilatation of all the sinuses takes place without rupturing and the prognosis is good. These aneurysms are, without question, congenital in origin but should be clearly distinguished and separated because their appearance is entirely different, and because they are not amenable to surgical treatment.

Aneurysms of the sinus of Valsalva are frequently associated with coarctation of the aorta.[48-41] Whether the high blood pressure is the chief factor in their development

or whether they arise from some latent congenital lesion is yet unclear because no detailed descriptions have been given

Despite the great variation in the types of aneurysms which originate in the sinus of Valsalva, and their completely different symptomatology and prognosis they have been dealt with indiscriminately in the literature, and this has caused no small amount of confusion. Both congenital and acquired etiological factors which are combined in a complicated fashion are responsible for the formation of aneurysms of the sinus of Valsalva. To gain a clear understanding of any lesion one must consider the processes involved in its development In Table I the congenital and acquired etiological factors together with the various types of aneurysms of the sinus of Valsalva, have been arranged to provide a clearer insight into this problem. Those cases which are amenable to surgical therapy belong to the group of congenital aneurysms in the narrow sense of that term. The reported cases belong predominantly in this group and those that are considered as congenital aneurysms in this presentation belong to this category

Classification

Only those cases of congenital aneurysm of the sinus of Valsalva for which there were relatively good postmortem descriptions of the topography were selected and listed in Table II The top horizontal section of the Table gives the name of the sinus from which the aneurysm originated the site and the direction of projection. The presence or lack thereof of associated ventricular septal defects and if present, the type of defect are listed in the left-hand vertical column. This series

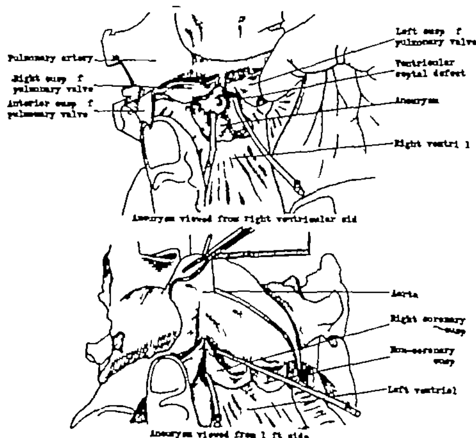


Fig 15 Ruptured aneurysm of sinus of Valsalva of Type I. Case 4 32 year-old man. Sound A passes through aneurysm from right ventricle to aorta. Sound *B* passes through ventricular septal defect from right ventricle to left ventricle.

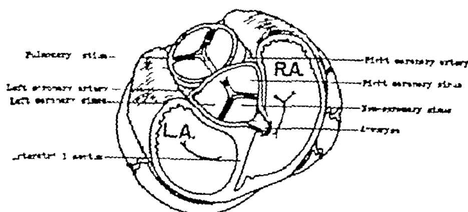
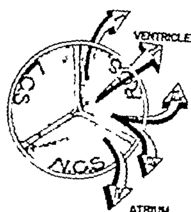


Fig. 16. Semischematic drawing of aneurysm of sinus of Valsalva of Type IV.



Types	Number of cases
I	5
Ivsd	17
II	2
IIvsd	1
IIIv	3
IIIv vsd	1
IIIa	11
IIIa vsd	0
IV	11
IVvsd	1

Fig. 17. See text.

includes 2 cases of bicuspid aortic valves; these cases were included because the presence of a rudimentary ridge made it possible to distinguish the right coronary sinus or noncoronary sinus. These 2 cases are indicated in the table by an asterisk. To show from which part of the sinus the aneurysm developed, each sinus was divided into three equal parts, to which were given the names shown in Fig. 13.

Of course, the parts from which the aneurysm originated could not be determined so accurately as shown in the diagrams, and it should be noted that when the opening of the aneurysmal sac appeared to be nearer to one part, this part was used for the purposes of the table. The ventricular septal defects were classified according to those immediately below the pulmonary valve, those in the crista supraventricularis, and those in the membranous septum.

It will be seen in Table II that the various aneurysms were divided into four large groups, Types I, II, III, and IV. The criteria used for this classification were the altered *hemodynamics after rupture of the* aneurysm, the characteristic symptoms, and the prognosis. The Type III group was subdivided into Types IIIv and IIIa, according to whether the aneurysm was projected into the right ventricle or into the right atrium, respectively. High ventricular septal defect is *frequently* associated

with the Type I aneurysm. This combination of malformations is denoted by *Ivsd*. The Type I aneurysm and high ventricular septal defect are not an accidental combination of two malformations but are derived from the same cause. Similarly, *IIvsd* indicates the combination of a Type II aneurysm and a ventricular septal defect at the crista supraventricularis. *IIIv vsd* indicates a combination of a Type IIIv aneurysm and a ventricular septal defect of the membranous septum and *IVvsd* signifies a combination of a Type IV aneurysm and ventricular septal defect of the membranous septum. The combination of a Type I aneurysm and a ventricular septal defect of the membranous septum was considered to be accidental since no common cause was demonstrable and, therefore, such a condition was not included in this classification.

Type I. Most of the cases of congenital aneurysms of the sinus of Valsalva reported in Japan are of Type I. This type of aneurysm develops in the left part of the right coronary sinus and projects into the outflow tract of the right ventricle (Figs. 14 and 15). As many as 82 per cent of the aneurysms in this group are associated with high ventricular septal defects (Type Ivsd).[illegible] Aneurysms of Type I are relatively rare since only 3 cases[illegible] have been reported in Japan, and still rarer in Western countries, since only 2 cases[illegible] have been found. The aneurysms in this group vary in size from a slight dilatation to a pouch of about the size of a cherry.

Type II. Aneurysms of Type II are exceedingly rare; only one case, that of Edwards[11] has been reported. Operation in one case belonging to this group was successfully carried out recently in our hospital.[34] An Ivalon patch was placed from the aortic side to the right ventricular margin with complete closure and cure. On the basis of the picture presented in Kirklin's report,[9] the aneurysm in his patient appears to be Type IIvsd.

Type III. Aneurysms which originate from the posterior part of the right coronary sinus have been designated as *Type III*. Fifteen cases have been described in the foreign literature but none has been reported in our country. Type III aneurysms which project into the right ventricle behind the septal leaflet of the tricuspid valve after penetrating the membranous septum are classified as Type IIIv. This type is not frequently encountered since only 3 cases have been reported.[illegible] White[illegible] described a case with an opening of the ventricular septal defect of the membranous septum next to an aneurysm of Type IIIv which could be described as Type IIIv vsd. Type III aneurysms which bulge out into the right atrium are classified as Type IIIa.[illegible] The aneurysms of this group are usually about the size of the tip of the little finger but may, in a rare case, lengthen and rupture into the right ventricle after passing through the tricuspid ostium as reported by Hirschboeck.[illegible]

Type IV. Aneurysms which form in the right part of the noncoronary sinus, that is, the part adjacent to the right coronary sinus are grouped as Type IV. This type has been reported frequently in Western countries,[illegible] but only one case, which we reported, has been encountered in Japan. Similar to Type IIIa, this type frequently protrudes near the commissure of the septal and anterior leaflets of the tricuspid valve. It may sometimes bulge out near the commissure of the septal and posterior leaflets of the tricuspid valve, as in our case and in that reported by Peltzer.[illegible] This is due to individual variation in the degree of rotation of the great vessels and in the expanse of the membranous septum. Fig. 16 is a schematic drawing of the Type IV aneurysm. Although the aneurysm is usually about the size of the tip of the little finger, it may lengthen and rupture into the right ventricle after passing through the tricuspid ostium as in the case described by Peltzer.[illegible]

The foregoing classification is summarized in Fig. 17.

Conclusion

A classification of the various congenital aneurysms of the sinus of Valsalva has been attempted with due attention given to the different morphologic types. It is believed that this classification will be useful to the clinician since the symptoms, prognosis, and surgical techniques differ for each type. Because the number of cases

is still limited further evaluation of this classification is planned and more reported cases will be added to Table II The symptoms and prognosis of and the surgical and diagnostic methods applicable to each type will be presented at a later date.

REFERENCES

1. Thurnam J On aneurysms, and especially spontaneous aneurysms of the ascending aorta, and sinus of Valsalva Med.-Chir Tr 23:323 1840
2. Bigelow W G and Barnes, W T Ruptured aneurysm of aortic sinus, Ann. Surg 150:117 1959
3. McGoon D C., Edwards, J E., and Kirklin, J W Surgical treatment of ruptured aneurysm of aortic sinus, Ann. Surg 147:387 1958
4. Lillehei, C. W Stanley P and Varco, R. L. Surgical treatment of ruptured aneurysms of the sinus of Valsalva Ann. Surg 146:459 1957
5. Morrow A. G Baker R R Hanson, H F., and Mattingly T W Successful surgical repair of ruptured aneurysm of the sinus of Valsalva, Circulation 16:533 1957
6. Dubost, Ch., Blondeau, Ph. and Piwnica, A. Rupture des anévrysmes des sinus de Valsalva dans les cavités cardiaques, J Chir (Paris) 75:539 1958.
7. Sakakibara, S. Hattori J and Konno, S. Successful surgical repair of aneurysm of the sinus of Valsalva (in Japanese) Operation 14 723 1960
8. Kumiya T., Tanabe, H Kuribara H and Kuramoto, K.: A case of sinus of Valsalva-right ventricular fistula successfully repaired by surgery (in English) Jap. Heart J 1:239 1960
9. Walmsley T Quain's elements of anatomy ed. 11 New York, Longmans, Green & Company Cited by Oram and East.[13]
10. Ostrum H W., and Robinson, B D Aneurysm of the aortic sinuses of Valsalva Am. J Roentgenol. 40:828, 1938.
11. Edwards, J E and Burchell H B The pathologic anatomy of deficiency between the aortic root and the heart (including aortic sinus aneurysms) Thorax 12:125 1957
12. Gross, L., and Kugel, M A.: Topographic anatomy and histology of the valves in the human heart, Am. J Path 7:445 1931
13. Oram, S., and East T Rupture of aneurysm of aortic sinus into the right side of the heart, Brit. Heart J 17:541 1955
14. Feldman L. Friedlander J., Dillon, R., and Wallyn, R. Aneurysm of right sinus of Valsalva with rupture into right atrium and into the right ventricle Am Heart J 51:314 1956.
15. Abbott, M E. Clinical and developmental study of a case of ruptured aneurysm of the right anterior aortic sinus of Valsalva. Contributions to Medical and Biological Research (Osler Memorial) 2:899 1919
16. Jones, A. M., and Langley F A.. Aortic sinus aneurysm, Brit. Heart J 11:325 1949
17. Walcher K.: Ein Fall on zweiteiligen Aortenklappen mit Aneurysmen beider Sinus Valsalvae, Virchow Arch path Anat 231:73 1921
18. Higgins, A. R. Aneurysm of sinus of Valsalva with rupture into right auricle and death U S. Naval M Bull 32:417 1934.
19. Micks, R. H Congenital aneurysms of all three sinuses of Valsalva, Brit. Heart J 2:63 1940
20. Raman T K. and Menon, T B: Aneurysms of the sinuses of Valsalva Indian Heart J 1:1 1949
21. Venning G. R. Aneurysm of the sinus of Valsalva, Am Heart J 42:57 1951
22. Edwards, J E., Burchell H B and Christensen, N A. Specimen exhibiting the essential lesion in aneurysm of the aortic sinus, Proc. Staff Meet. Mayo Clin 31:407 1956.
23. Jacobi, M and Heinrich A Congenital aorticoventricular fistula with engrafted acute suppurative endocarditis, Am. J M Sc. 186:364 1933
24. Sakakibara S., and Konno, S. Unpublished data.
25. Livingston, B: Congenital communication between the right side of the heart and the beginning of the aorta, Med Rec New York 24:249 1883
26. White, W H A case of patent ventricular septum together with an aneurysm of the base of the aortic opening into the right ventricle, Tr Path Soc. of London 43:34 1892
27. Rickards, E. Six cardiac and vascular cases with remarks and engravings, Brit. M J 2 71 1881
28. Smith W A. Aneurysm of the sinus of Valsalva with report of two cases, J.A.M.A. 62 1878, 1914
29. Synder G A and Hunter W C. Syphilitic aneurysm of left coronary artery with concurrent aneurysm of a sinus of Valsalva, and an additional case of Valsalva aneurysm alone Am J Path. 10 757 1934
30. Schuster N H Aneurysm of the sinus of Valsalva involving the coronary orifice, Lancet 1:507 1937
31. Chipps, H D: Aneurysm of the sinus of Valsalva causing coronary occlusion, Arch Path. 31:627 1941
32. Kahn F H and Pearce, M L.: Aneurysm of two aortic sinuses A.M A. Arch Int Med. 100:126, 1957
33. Merten C. W., Finby N and Steinberg I The antemortem diagnosis of syphilitic aneurysm of the aortic sinuses report on 9 cases, Am. J Med. 20:345 1956.
34. Schmitt, K.: Tuberkuloeses Aneurysma der Aorta in Sinus Valsalvae Ztschr Kreislaufforsch 17 393 1958
35. Toshach, S and Bain G O: Acquired aortic sinus aneurysm caused by Hemophilus aphrophilus, Am J Clin Path. 30:328, 1958.
36. Jick, H and Kasarjian, P J Rupture of aneurysm of aortic sinus of Valsalva associated with acute bacterial endocarditis, Circulation 19 745 1959

37 Hall, B and Pickard S. D : Unsuspected rupture of aortic sinus aneurysm into the right atrium associated coarctation of aorta, bicuspid aortic valve aortic stenosis, and bacterial endocarditis, Am. J Cardiol. 3:404 1959
38. Orbison, J L., and Mostofi, F K. Hematoma of the interatrial septum AM. HEART J 51:636, 1956
39 Herrmann, G R., and Schofield, N D The syndrome of rupture of aortic root or sinus of Valsalva aneurysm into the right atrium AM. HEART J 34:87 1947
40. Kay J H Anderson, R. M Lewis, R. R., and Reinberg M Successful repair of sinus of Valsalva-left trial fistula, Circulation 20:427 1957
41 Hart, K. Über das Aneurysma des rechten Sinus Valsalvae der Aortae und seine Beziehungen zum oberen Ventrikelseptum Virchows Arch. path. Anat. 182 167 1905
42. Warthen, R. O Congenital aneurysm of right anterior sinus of Valsalva (interventricular aneurysm) with spontaneous rupture in left entricle, AM. HEART J 37:975 1949
43 Tanaka, S., Yoshikoshi, Y Seki, K., Koide, K., Ogata, E., and Nakamura, K.: Congenital aneurysm of the right coronary sinus of Valsalva with rupture into the left ventricle, Jap. Heart J 1 106, 1960.
44 Moses, M F Aortic lesions associated with arachnodactyly Brit. M J 2:81 1951
45. Steinberg, I., and Geller W Aneurysmal dilatation of aortic sinuses in arachnodactyly diagnosis during life in three cases, Ann. Int. Med. 43 120, 1955
46. Steinberg I Clinical manifestations of the unruptured aortic sinus aneurysm, Circulation 14 115 1956.
47 Steinberg, I Mangiardi, J L., and Noble, W J.: Aneurysmal dilatation of the aortic sinuses in Marfan's syndrome, Circulation 16:368, 1957
48. Dubiller W T ylor T L., and Steinberg, I Aortic sinus aneurysm associated with coarctation of aorta, Am. J Roentgenol. 73 10 1955
49 Steinberg, I., and Finby N Congenital aneurysm of the right aortic sinus associated with coarctation of the aorta and subacute bacterial endocarditis, New England J Med 253:549 1955.
50 Glenn, F Stewart, H J Engle, M A., and Steinberg I Coarctation of aorta complicated by bacterial endocarditis and an neurysm of the sinus of Valsalva Circulation 17:432, 1958.
51 Steinberg, I., and Sammons, B P Aneurysmal dilatation of the aortic sinuses in coarctation of the aorta report of two new cases and review of the literature Ann. I t. Med 19:922, 1958.
52. Bristow J D Parker M and Haug, W A. Hemopericardium following rupture of a bacterial aortic sinus aneurysm, Am J Cardiol. 6:355 1960
53. Weiss, L Rupture of an aneurysm of the right aortic sinus (of Valsalva) Brit. Heart J 19 138, 1957
54 Richards, E. Six cardiac and vascular cases with remarks and engravings, Brit. M. J 2:71 1881
55 Morgan, E. H and Burchell, H B Ventricular septal defect simulating patent ductus arteriosus, Proc. Staff Meet Mayo Clin. 25:69 1950
56. Burchell, H B and Edwards, J E. Aortic sinus aneurysm with communications into right ventricle and associated ventricular septal defect, Proc. Staff Meet. Mayo Clin 26:336, 1951
57 Suge, S., et al. Aneurysm of sinus of Valsalva ruptured into right ventricle case report (In Japanese) Respiration & Circulation 3:270 1955
58 Lin, T K Crockett, J E and Dimond E. G Ruptured congen tal aneurysm of the sinus of Valsalva, AM HEART J 51:445, 1956
59 Brofman, B L. and Elder J C Cardioaortic fistula (temporary circulatory occlusion as an aid in diagnosis) Circulation 16:77 1957
60. Oguro C., et al. Congenital neurysm of sinus of Valsalva ruptured into right ventricle (in J panese) Respiration & Circulation 5:443 1957
61 Shibuya, M et al. Ruptured congenital aneurysm of right sinus of Valsalva diagnosed during life (In Japanese) Respiration & Circulation 7:509 1959
62. Ishihara, T Postmortem finding of ruptured aortic sinus aneurysm (in Japanese) J Jap. Soc Int. Med. 44:319 1955
63 Sakakibara, S. Diagnosis of congenital and acquired heart diseases (in Japanese) Tokyo, 1958, Bunkodo & Company p. 341
64 Sakakibara S. Diagnosis of congenital and acquired heart diseases (in Japanese) Tokyo, 1958, Bunkodo & Company p. 344
65. Wigle, E. D., McKelvey A. D and Bigelow W G. Ruptured aneurysm of the sinus of V lsalva, Canad. M A. J 79:837 1958.
66. Brown, J W Heath, D and Whitaker W : Cardioaortic fistula a case diagnosed during life and treated surgically Circulation 12:819 1955
67 Krzywicki: Das Septum Membranaceum Ventriculorum Cordis, seine Verhältnis zum Sinus Valsalvae Dexter Aortae und die aneurysmatischen Veraenderungen bider Beitr path Anat. 6:465 1888.
68. Wright, R. B Aneurysm of a sinus of Valsalva with rupture into the right auricle Arch Path 23:679 1937
69 Macleod, A.: Cardioaortic fistula, Brit. Heart J 6 194, 1944.
70. Goehring C. Congenital aneurysm of the aortic sinus of V lsalv J Med Research 42:49 1920.
71 Duras, P Heart block with aneurysm of the aortic sinus Brit Heart J 6:61 1944
72. Kawasaki, I A., and Benenson A. S. Rupture of n aneurysm of a sinus of V lsalva into the right auricle, Ann. I t. Med. 25 150 1946
73. Maynard R. M and Thompson, C. W Congenital aneurysm of aortic sinus Arch Path 45:65 1948

onus may be utilized as a guide for passing the cardiac catheter through the ductus. Furthermore, in angiocardiograms of high quality the washout area at the junction of the main and left pulmonary arteries may be diagnostic, since a jet of unopacified blood passes through the patent ductus into the pulmonary artery diluting the contrast media at its point of entry. Similarly one may recall vivid angiographic pictures of a localized jet through the stenotic pulmonic valve and of the considerable swirling of light and dark in the dilated proximal portion of the pulmonary artery. Those who have had occasion to observe a dilated thin-walled pulmonary artery during thoracotomy in a subject with a large shunt may recall observing blood flow through the wall of the vessel, where waves of oxygenated and unoxygenated blood form phantasmagoric patterns of light and dark.

Data concerning the left side of the heart are also available. Indeed it is widely accepted that in the presence of an interatrial septal defect of the ostium secundum variety an indicator-dilution curve recorded peripherally after injection of indicator into the right pulmonary artery should show a larger *left-to-right shunt than a similar curve after injection* into the left pulmonary artery. This is because there is not complete mixing in the left atrium, and the right pulmonary veins, attached closest to the site of the interatrial communication, frequently deliver more of their contents into the stream which passes into the right atrium than do the left pulmonary veins.[4] However, there are well-documented instances in which, for no obvious reason, indicator injected into the left pulmonary artery appears to recirculate more than that injected into the right *pulmonary artery. No other explanation is available*, at present, than that some peculiar stream in the left atrium carries blood from the left pulmonary veins through the atrium and across the septal defect, whereas blood from the right pulmonary veins passes down into the left ventricle and out to the systemic circuit. Furthermore, in the presence of an atrial septal defect indicator-dilution curves recorded after injection into the left atrium may show no indication of a left-to-right shunt, since all of the dye may be caught in the stream of blood *which passes directly through* the mitral valve and is carried into the left ventricle. Similarly, in the presence of mitral insufficiency when contrast substance is injected into the left ventricle, one may observe a thin jet of dense contrast substance squirting back through the valve. Depending upon its size and the force with which it is regurgitated, the jet may spread in a mushroom-shaped cloud of ever-decreasing density throughout the left atrium, or it may be carried essentially undiluted through the left atrial cavity and impinge on the posterior wall of the cavity, becoming disseminated at that point. The taking of samples at multiple points in the left atrium has established that in mitral insufficiency such streams also occur when indicator substance is injected into the left ventricle.

Similar information may be found concerning the left ventricle. Thus, it has been demonstrated that saline solution injected into the left ventricle and sampled at different sites indicates incomplete mixing. Results of similar tests for completeness of left ventricular mixing after injection into the left atrium indicated that mixing was incomplete even under these circumstances.[4] In subjects with tetralogy of Fallot when cineangiocardiography is done with injection into the right ventricle, it is almost routine to see contrast substance pass over the cephalic brim of the ventricular septum through the ventricular septal defect and into the outflow tract of the left ventricle. When left ventricular systole occurs, this mass of contrast substance is carried out into the aorta. Depending upon the site of injection, the volume of the right-to-left shunt and the size of the interventricular septal defect, the mass *of contrast substance which crosses the* septum may or may not pass far enough down into the left ventricle to outline the septum completely. In some cases, one may see the entire septum, but in others only its upper portion, since there is such incomplete mixing in the left ventricle that only the outflow tract is visualized. Similarly, when contrast substance is injected above the aortic valve in the presence of aortic insufficiency, one may see only a slight wisp of regurgitation into the outflow tract of the left ventricle or in other cases, *a large mass may pass through the aortic valve and* down to the apex of the left ventricle. With injections of contrast material into the left ventricle itself it is frequently possible to see the negative shadow of a mass of blood pass through the mitral valve and out of the aorta without ever mixing adequately with the intraventricular contrast substance. This observation has been used as an explanation for the failure of an indicator-dilution curve recorded from the aortic root to show an even systolic plateau. One might add that the plateau *on an indicator-dilution curve obtained by sampling* at the root of the aorta or pulmonary artery if diastolic may well be construed as the result of the fact that during diastole there is essentially no flow in this region. If the system is stable, the immediate result of no flow should be that the same concentration of indicator is measured until more flow occurs, i.e., with the next systole. If a good plateau occurred during systole, one might well have evidence that mixing is good in the left ventricle, but this is not what has been demonstrated. Indeed, if systole and diastole were indicated one might well use some of the curves which have been used to calculate end-systolic and end-diastolic volume in the ventricle, to show either (a) that there is not complete mixing in the left ventricle, and, hence, there is considerable variation in the concentration of indicator passing the sampling site during systole or (b) that the system used for recording the indicator-dilution curve is not sufficiently good to reveal a plateau which may exist during systole, and hence, is inadequate to be of value in solving the problem.

It would seem to this observer that the time has come to face the fact that instantaneous, or complete, mixing is a myth. It does not seem that further progress can be made by more complicated analyses of indicator-dilution curves based on this myth. For those who are inclined to use information derived from indicator-dilution studies in a reasonable fashion, such an unreasonable basic assumption is not required, and the ends of truth and science

would seem to be served better by the ready admission that instantaneous mixing is never achieved, and that under the worst circumstances there is very poor mixing indeed.

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REFERENCES

1. Barclay, A. E., Franklin, K. J., and Prichard, M. M. L.: The foetal circulation, Springfield, Ill., 1945, Charles C Thomas, Publisher.
2. Lind, J., and Wegelius, C.: Atrial septal defects in children, an angiographic study, Circulation 7:819, 1953.
3. Amorim, D. S., Weidman, W. H., and Wood, E. H.: Use of indicator-dilution curves for selection of site for injection of contrast medium for selective angiocardiography, Proc. Staff Meet. Mayo Clin. 35:756, 1960.
4. Silver, A. W., Kirklin, J. W., and Wood, E. H.: Demonstration of preferential flow of blood from inferior vena cava and from right pulmonary veins through experimental atrial septal defects in dogs, Circulation Res. 4:413, 1956.
5. Woodward, E., Jr., Swan, H. J. C., and Wood, E. H.: Evaluation of a method for detection of mitral regurgitation from indicator-dilution curves recorded from the left atrium, Proc. Staff Meet. Mayo Clin. 32:525, 1957.
6. Irisawa, H., Wilson, M. F., and Rushmer, R. F.: Left ventricle as a mixing chamber, Circulation Res. 8:183, 1960.
7. Swan, H. J. C., and Beck, W.: Ventricular nonmixing as a source of error in the estimation of ventricular volume by the indicator dilution technic, Circulation Res. 8:989, 1960.

Role of the pericardium in the application of the Starling mechanism to unanesthetized animals

Renewed interest in regard to the validity of the Frank-Starling mechanism in the intact healthy heart was stimulated chiefly by the challenging observations of Rushmer. Using an elegant technique of continuously recording various parameters of ventricular performance in unanesthetized dogs, Rushmer noted that during muscular exercise or intravenous infusions of blood there was either no change or very slight increase in end-diastolic diameter (assumed to be closely related to volume) of the left ventricle.[1,2] Furthermore, the classic concept that stroke volume increases appreciably during muscular activity was not confirmed either in unanesthetized dogs or in man with the use of more reliable methods of determining cardiac output.[3-5] Some investigators[6] have confirmed the latter observation, whereas others have failed to do so. The reasons for this discrepancy are still obscure.

In explaining his findings, Rushmer has emphasized the important role of neural and hormonal influences on the performance of the intact heart in masking or obscuring the Starling mechanism, but the possible contribution of the pericardium has not received adequate attention. In the excellent textbook of Rushmer[1] there is practically no discussion of the functional significance of the pericardium. Also, during the 1955 Symposium on the Regulation of the Performance of the Heart, the role of the pericardium in affecting the diastolic volume of the intact heart has been somewhat overlooked. Katz[8] has listed four basic factors that determine the end-diastolic blood volume of the ventricles. To those might be added another factor for the intact heart, namely, the capacity and distensibility of the pericardium. Most of the studies on the Starling mechanism were carried out on isolated hearts in which the pericardium had been cut open, giving full freedom for the ventricles to distend. However, Sarnoff,[9] realizing the importance of this structure, demonstrated the "Starling curve" in open-chest dogs before and after opening the pericardium.

Although considerable work has been done on the function of the pericardium in limiting acute distention of the heart,[10-12] this role has not been given sufficient attention in connection with the observations of Rushmer in the unanesthetized animal. In 1925 Beck[13] studied the size of the heart in pericardiectomized dogs before and immediately after strenuous exercise. However, no observations were made during exercise, and since postural changes profoundly alter diastolic dimensions of the heart, it is difficult to draw conclusions from such experiments.

In view of all this, it would be important to have data on ventricular performance obtained by refined methods such as those of Rushmer in unanesthetized animals from which the pericardium has been removed. Such studies may shed more light on our understanding of the differences between the responses of the isolated and the intact normal ventricles to various forms of physiologic stress.

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REFERENCES

1. Rushmer, R. F.: Applicability of Starling's law of the heart to intact unanesthetized animals, Physiol. Rev. 35:138, 1955.
2. Rushmer, R. F., Smith, O., and Franklin, D.: Mechanisms of cardiac control in exercise, Circulation Res. 7:602, 1959.
3. Rushmer, R. F.: Constancy of stroke volume during exercise, Am. J. Physiol. 196:745, 1959.
4. Rushmer, R. F.: Postural effects on the base lines of ventricular performance, Circulation 20:897, 1959.
5. Rushmer, R. F., and Smith, O. A., Jr.: Cardiac control, Physiol. Rev. 39:41, 1959.
6. Wang, Y., Marshall, R. J., and Shepherd, J. T.: Stroke volume in the dog during graded exercise, Circulation Res. 8:558, 1960.
7. Ballie, M. D., Robinson, S., Rostorfer, H. H., and Newton, J. L.: Effects of exercise on heart output of the dog, J. Appl. Physiol. 16:107, 1961.
8. Rushmer, R. F.: Cardiac diagnosis, a physiologic approach, Philadelphia, 1955, W. B. Saunders Company; second edition, 1961, Cardiovascular dynamics.
9. Katz, L. N., Sarnoff, S. J., Guyton, A. C., Gregg, D. E., Lasber, V., Rushmer, R. F., Gauer, O. H., Richards, D. W., and Hamilton, W. F.: Symposium on the regulation of the performance of the heart, Physiol. Rev. 35:91, 1955.
10. Berglund, E., Sarnoff, S. J., and Isaacs, J. P.: Ventricular function. IV. Role of the pericardium in regulation of cardiovascular hemodynamics, Circulation Res. 3:133, 1955.
11. Kuno, Y.: The significance of the pericardium, J. Physiol. 50:1, 1915-16.
12. Beck, C. S., and Moore, R. L.: The significance of the pericardium in relation to surgery of the heart, Arch. Surg. 11:550, 1925.
13. Wilson, J. A., and Meek, W. J.: The effect of the pericardium on cardiac distention as determined by the x-ray, Am. J. Physiol. 82:34, 1927.
14. Carleton, H. M.: The delayed effects of pericardial removal, Proc. Roy. Soc. London, Series B 105:230, 1929.
15. Fineberg, M. H.: Functional capacity of the normal pericardium, Am. Heart J. 11:748, 1936.
16. Hefner, L. L., Coghlan, H. C., Jones, W. B., and Reeves, T. J.: Distensibility of the dog left ventricle, Am. J. Physiol. 201:97, 1961.

Diffuse hyaline pulmonary disease of foals and infants

An interesting study originates from the field of veterinary medicine which should have implications in man. Mahaffey and Rossdale[1] describe an acute convulsive syndrome which is common (1 per cent of births) in foals delivered by veterinary physicians but rare among those unattended by man. The convulsions develop soon after birth (less than 12 hours) after a normal simple delivery in a normal foal. Then when the animal stands or attempts to stand, convulsive movements begin in the head and feet and the animal falls. It may emit a barking noise and a generalized convulsion may ensue. If treated and nursed carefully, recovery is about 50 per cent and without residual effects. There may be temporary blindness.

Premature human infants and those delivered by Caesarean section often present a syndrome (pulmonary syndrome) very similar to that described above for foals.[1] Immediately after birth the infants appear to be normal but they soon develop respiratory distress associated with respiratory noises. About 31 per cent develop convulsions, and 10 per cent have signs of cerebral irritation.[1] The infant becomes restless, irritable and utters a high pitched cry; there is jerkiness of the muscles and convulsions.

[illegible] for the lungs of both the infants and the newborn foals which die of pulmonary syndrome are strikingly similar. The lungs are voluminous and dark purple in color. The cut surface of the lung resembles fetal liver, being dark and solid in appearance. Microscopically there is extensive resorption atelectasis and complete disappearance of the normal alveolar pattern. No other pathologic lesions have been demonstrated in either the infants or the animals.

The mechanism of this syndrome is not clearly understood, but it appears that too early ligation of the umbilical cord is the important etiological factor. Under natural and normal circumstances, unattended by man, the mare will rest for 30 minutes after delivery. During this period the foal remains inactive. The cord is then broken when the foal or the mare moves. Previous to this all of the blood (1,020 to 1,500 c.c.) in the placenta is squeezed into the foal. When the veterinary physician ligates the cord immediately after birth, the newborn is deprived of this blood.

Mahaffey and Rossdale[1] have studied puppies and rabbits and produced similar lesions in the lungs by ligating the cord immediately after delivery.

This interesting syndrome as well as the influence of a reduced volume of blood on the lungs, brain, eyes and general physiology of mammals, including

man, at the time of lung expansion after birth needs study. Blood volume and the systemic and pulmonary circulations have been studied very little at and immediately after birth or before and after ligation of the umbilical cord.

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REFERENCES

1. Mahaffey, L. W., and Rossdale, P. D.: A convulsive syndrome in newborn foals resembling pulmonary syndrome in the newborn infant, Lancet 1:1223, 1959.
2. Bound, J. P., Butler, N. R., and Spector, W. G.: Classification and causes of perinatal mortality, Brit. M. J. 2:1191, 1956.

Book reviews

KLINISCHE ELEKTROKARDIOGRAPHIE. By Prof. Dr. Max Holzmann, Privatdozent an der Universität Zürich, ed. 4. Stuttgart, 1961, Georg Thieme, 889 pages, 386 illustrations. Price DM 87.

The fourth "enlarged and improved" edition follows the third edition after an interval of 6 years. About 200 pages have been added without any essential change in the structure of the book.

A volume of 900 pages has the character of a reference book, not meant to be read from the first to the last page. However, it is difficult to use the book as basis for reference, since the literature is cited at the end of each of the numerous sections and an authors index is absent.

The book has 13 chapters: (1) history, (2) instruments and methods, (3) the anatomic basis, (4) the electrophysiologic basis, (5) the normal EKG, (6) the abnormal EKG, except arrhythmias, (7) arrhythmias, (8) Wolff-Parkinson-White syndrome, (9) EKG and heart trauma, (10) EKG in congenital heart disease, (11) EKG in heart tumor, (12) EKG in neuromuscular disease, (13) the dying heart. Chapter 6, with 370 pages, and Chapter 7, with 270 pages, are the largest. The electrophysiologic background, the various types of abnormal ventricular complexes, and arrhythmias are well presented, with numerous (386) excellent illustrations. The topographical location of myocardial infarction is illustrated by diagrams, probably on the basis of electrocardiographic patterns. There are no photographic illustrations of autopsied infarcted hearts with corresponding ECG findings, which would be preferable in view of the large existing material on correlation between autopsy data and electrocardiographic patterns in myocardial infarction (for instance, the series of Gordon Myers or that of George Burch and associates).

The normal ECG and abnormal ventricular complexes are explained as projections of spatial vectors, and the concept of "unipolar electrocardiography" is abandoned. This certainly conforms to recent knowledge, but the construction of vectors from conventional leads is limited to the frontal and horizontal planes while true spatial vectors are not determined. This limitation may be justified for a book on clinical electrocardiography. Nevertheless, with the emphasis given vectorial interpretation, a condensed discussion of corrected orthogonal lead systems which were developed during the past 6 years would have been desirable as general information for the reader.

Electrocardiography has grown to such an extent that no longer can any individual author be competent in all its ramifications and applications. For example, the discussion of exercise tests is not adequate. No precise criteria for an abnormal response are given; the exercise used by the author (stair climbing) cannot be satisfactorily standardized and it may involve too great a risk for wide clinical application. Master's two-step test (including the double two-step test) is, according to Holzmann, insufficient to produce coronary insufficiency or angina pectoris and therefore not suitable as a diagnostic method. This comment reveals unfamiliarity not only with the actual clinical application of Master's two-step test, but also with the large literature.

The book exceeds the realm of electrocardiography and includes prognosis and therapy. However, the ECG alone is not a sufficient base for adequate discussion of therapy, and this reviewer thinks that omission of these aspects would result in a desirable concentration and reduction of the volume. The criticism, however, should not detract from the considerable merits of the book, which seems to have been well accepted in Europe.

THE STAGES OF HUMAN DEVELOPMENT BEFORE BIRTH. AN INTRODUCTION TO HUMAN EMBRYOLOGY. By E. Blechschmidt, M.D., Professor of Anatomy and Director of the Institute of Anatomy, University of Göttingen. Philadelphia, 1961, W. B. Saunders Company. 684 pages, 7 tables, 579 figures. Price $23.

The subtitle of the volume, "An Introduction to Human Embryology," might suggest that it is a textbook. Instead, the work is designed as an atlas which contains only condensed text matter to accompany the numerous illustrations and their legends. For the most part, the illustrations are drawings, photomicrographs, and gross photographs that appear for the first time in this volume. All are of excellent quality.

A distinctive feature of the atlas is its bilingual character. The pages of descriptive text are in two-column format, German in the left column and English in the right one; figures are on the facing page, carrying both German and English legends and both also for labels when the terms are not in international usage. Likewise, there are two prefaces, two statements of acknowledgment, two tables of contents, two introductions, two glossaries of special terms, and two indexes. All this may have been planned for the respective language groups so that a single volume and its one set of illustrations would serve both. The plan seems awkward for the reader and it adds to the cost of the volume. However, the parallel texts in two languages afford a good opportunity for persons more accustomed to one of these languages to improve his reading knowledge of the other. Graduate students, for example, could profit from use of the book for this purpose.

The preface, in outlining the aims of the book, makes several rather misleading statements or implications: (1) It is stated that until "very recently" the earliest stages of human development were not known. This would be true if the frame of reference of "very recently" is the long history of human embryology, but the classic studies of Hertig and Rock have been incorporated in standard textbooks for a considerable term of years. (2) The topographical

anatomy of embryos, it is stated, could not be investigated "because appropriate methods, especially useful reconstruction practices, has been lacking." In 1883 Born published an account of his method of reconstructing objects in microscopic serial sections, and the method has been in wide use ever since. Indeed the author includes Born's method in a series of 32 landmarks of embryologic history which begins with de Graaf in 1672. (3) "To describe their [embryonic] development as movement had not been taken into serious consideration. It had not been supposed that this could reveal the regularity and coherence of development." No comment on this obviously incorrect description of current textbooks in human embryology is needed, beyond pointing out that the limitations of an atlas are such as to provide little opportunity for treating developmental mechanics.

Readers of the *American Heart Journal* may be particularly interested in commentary on the account of cardiac embryology. The 12 page section on the heart carries 18 illustrations, and of course some figures in other sections pertain in part to the heart. This compares with one of the standard American texts on human embryology in which the comparable material is covered in 22 pages with 53 illustrations in the section here, too, some figures elsewhere are relevant in part.

It is difficult to find a niche for this book in a working library. The letterpress does not unfold the story of embryologic development in the connected manner that is imperative in a textbook. The illustrations form a class but the available texts also are abundantly illustrated. Accordingly, the only evident function that the book can serve, in addition to the language training mentioned above, is to supplement the already existing atlases provided in standard textbooks.

Human Genetics (British Medical Bulletin, Volume 17, Number 3, September 1961). Edited by A. C. Stevenson, London, 1961, Medical Department, The British Council, 261 pages. Price $3.25.

This volume contains fifteen well-illustrated papers from a symposium on human genetics by British investigators who were selected for competence in their fields of active research. The areas of human genetics covered are of particular interest to the medical researcher and clinician who must work with individuals who are representative of the one-in-twenty births which result in some malformation (genetic or chromosomal) or which result in one of the 1,000 or more diseases or syndromes caused by known major mutant genes. A. C. Stevenson reviews average frequencies and mutation rates for types of clinical genetic entities, without being specific about any one condition. Emphasis throughout the book is on recent work in cytogenetics (six papers), biochemical genetics (five papers), quantitative and anthropological genetics (two papers), and clinical genetics (one paper).

The first paper by C. E. Ford on human cytogenetics is especially well done and covers the history of human chromosomal work, types and causes of chromosomal aberrations encountered, their frequency, and relations to specific clinical pathology. The other papers likewise are outstanding for their comprehensive yet concise, authoritative and well-documented summaries and organization of material. The five other papers on cytogenetics cover mongolism (L. S. Penrose), inherited variations of leukocytes (William M. Davidson), indirect assessment of number of X-chromosomes (Bernard Lennox), Turner's syndrome and allied conditions (P. E. Polani), and cytogenetics of abnormal sexual development (D. G. Harnden and Patricia A. Jacobs). Biochemical genetics is represented by work completed or in progress on galactosemia (A. Holzel), inherited variations of human plasma proteins (H. Harris), aminoaciduria (L. I. Woolf), pseudocholinesterase (H. Lehman, E. Silk, and J. Liddell), and pharmacogenetics (David A. Price Evans and C. A. Clarke). The remaining papers are on multifactorial inheritance in relation to human traits (J. A. Fraser Clarke), quantitative genetics of fingerprint patterns (Sarah B. Holt), and inheritance of congenital pyloric stenosis (C. O. Carter).

Since it would be impossible for a single symposium to cover all areas of current research in human genetics, the organizers of this symposium have wisely limited their selection of topics to timely subjects which relate to many clinical disciplines. The reader should bear in mind that similar treatment could have been given to hundreds of clinical conditions which are of special interest to the neurologist, ophthalmologist, dermatologist, and those in practically all other disciplines in clinical medicine. Topics such as blood groups, linkage, twin studies, etc., are not emphasized. When the reader realizes that this book gives only samples of model presentations representative of many approaches to human genetics, he will be aware of the tremendous scope and explosive penetration of this recently emphasized discipline into practically all aspects of clinical medicine.

Taschenbuch der Digitalis-Therapie. By Roland Nedner. Dannenberg/Elbe. Stuttgart, 1961, Georg Thieme. 117 pages. Price DM 16.80 ($4.20).

This little book was written as a guide to the practicing physician. The author discusses briefly the chemical structure and the degradation and elimination of cardiac glycosides as well as the effects of these glycosides on cardiac contractility, metabolism, and ion fluxes. The major part of the book contains a discussion of the therapeutic application of these glycosides. The modes of administration, dosage, the problem of cumulation and rate of elimination as well as indications and failures of glycoside therapy are discussed in some greater detail. The last part of the book contains some guiding data on

digitalizing and maintenance doses, and absorbability from the gastrointestinal tract of a number of clinically useful cardiac glycoside preparations.

This book summarizes a considerable amount of useful practical experiences with a number of glycoside preparations and will be useful to those who are beginning their career in the therapeutics of heart failure.

Announcements

The Leukemia Society, Inc. announces a program of 5-year support for CAREER INVESTIGATORS IN LEUKEMIA RESEARCH. An award of $15,000 per annum will be awarded for 5 years, renewable to 10 years, to qualified investigators in basic science or clinical departments of medical schools, universities, and research institutes.

The Leukemia Society Scholar whose research is broadly related to the problem of leukemia is expected to serve as a regular member of the faculty or staff of his institution.

Nominations for 1962-1963 should be submitted no later than April 1, 1962, to the Medical Director, Leukemia Society, Inc., 405 Lexington Ave., New York 17, N. Y. All material should be submitted in 5 copies and include a small photograph.

A postgraduate symposium on HEART DISEASE IN INFANCY will be held at the State University of New York Downstate Medical Center, Brooklyn, N. Y., from 9 A.M. to 5:15 P.M., Wednesday, March 14, 1962. The program will be sponsored by the Department of Pediatrics. There is no fee.

The symposium will be held in the First Floor Lecture Hall of the Basic Sciences Building of the Downstate Medical Center, 450 Clarkson Ave., Brooklyn, N. Y.

THE FOURTH ANNUAL CONFERENCE ON OPERABLE HEART DISEASE of the Presbyterian Medical Center will take place in San Francisco, Calif., on March 2 and 3, 1962.

The Conference will consist of 4 half-day sessions: (1) Diagnosis, (2) Technical Considerations, (3) Congenital Heart Disease, (4) Acquired Heart Disease.

For details and information contact Dr. Frank Gerbode, Conference Chairman, Presbyterian Medical Center, San Francisco 15, Calif.

Dr. William B. Kouwenhoven, professor emeritus and lecturer in surgery, The Johns Hopkins University, Baltimore, Md., has been awarded the 1961 EDISON MEDAL, the American Institute of Electrical Engineers announced on Dec. 22, 1961. The Medal was presented to the noted researcher in cardiac fibrillation at the Winter General Meeting of the American Institute of Electrical Engineers at the Statler Hilton Hotel, New York City, Jan. 29, 1962.

The College of American Pathologists announces that it will conduct A NATIONAL BLOOD SERUM CHOLESTEROL SURVEY.

The measurement of serum cholesterol as presently practiced is admittedly unsatisfactory because of wide variations in results. This variability is attributable to the use of diverse methods, and to the unavailability of an acceptable universal standard.

The estimation of serum cholesterol, long used in the study of diabetes, nephritis, and disorders of the liver, has become of added importance in recent years because of the relation of cholesterol metabolism to atherosclerosis and heart disease. The need for a procedure which will give reproducible results from place to place and from year to year is imperative.

It is the purpose of the Standards Committee of the College of American Pathologists to characterize a best cholesterol standard for universal use and to recommend an analytical procedure which may serve as a consistent point of reference.

This national preliminary survey of serum cholesterol estimations is being organized to disclose the present status of this chemical procedure. All laboratory directors and pathologists in the United States will be invited to participate.

Inquiries may be addressed to Cholesterol Survey, College of American Pathologists, Prudential Plaza, Chicago 1, Ill.

American Heart Journal

April 1962 Volume 63 Number 4

Editorial

Blood pressure and longevity

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The problem of defining levels of blood pressure which in themselves are significant has concerned physicians since the turn of the century. Routine recording of blood pressures increased gradually after 1896, when *Riva Rocci* made it a practical procedure through the use of the pneumatic cuff. By the nineteen twenties the determination of blood pressure had become a routine part of physical examinations and was widely required in examinations for life insurance.

The thought that blood pressure *normally* increases with age has been widely accepted for many years. There has been wide variation in levels considered to be normal, although the question of what is "normal" is not always easy to answer. We may think of "normal" in three ways: as "average," associated with normal life expectancy, or not evidencing signs of disease. If we think in terms of averages, we will often be disappointed because averages are not necessarily normal. For example, life insurance studies on weight indicate that, in general, weights 15 to 20 pounds below the average are associated with the most favorable life expectancy (lowest mortality). This is similarly true for blood pressure. Systolic blood pressures which are 10 to 15 mm. Hg below average, and correspondingly lower diastolic blood pressures are those associated with the greatest life expectancy.

Physicians are prone to think of normality as absence of definite signs or symptoms of disease. *They will, however, often* consider as significant preclinical conditions such as overweight and elevated blood pressure when these conditions are known to be associated with increased mortality. As the result of a number of large-scale follow-up studies, it appears that slight *elevations in* blood pressure *not accompanied* by signs or symptoms of disease are associated with shortened life expectancy.

The largest statistical study ever undertaken on data related to health is the Build and Blood Pressure Study, 1959, which analyzed data on almost 4,000,000 insurance policies covering the period 1935 to 1954. Some important aspects of that study in relation to blood pressure were the determination of average blood pressures and the effect on mortality of increased blood pressure, and of combinations of blood pressure and certain impairments (e.g., slight overweight, albuminuria, family history of cardiovascular disease). An interesting observation in the study was the concentration of systolic readings at the levels of 120, 130, and 140 mm. Hg, and dias-

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*Director, White Plains Medical Services, General Foods Corporation.

Table I. Average blood pressures

Ages	Men		Women	
	Systolic (mm. Hg)	Diastolic (fifth phase—mm. Hg)	Systolic (mm. Hg)	Diastolic (fifth phase—mm. Hg)
15-19	117	71	114	70
20-24	119	73	115	72
25-29	121	75	117	73
30-34	122	76	118	74
35-39	123	77	120	75
40-44	124	78	123	76
45-49	126	78	126	78
50-54	128	79	128	79
55-59	130	79	131	80
60-64	132	80	134	81

tolic readings at levels of 70 and 80 mm Hg. This reflected the tendency of physicians to report blood pressure readings in round numbers.

On the basis of the distribution of great numbers of blood pressure readings by age, average blood pressures were determined in the Build and Blood Pressure Study 1959; these are shown in Table I.

These indicate that average systolic pressures of men increase from 117 mm. Hg in the teens to 132 mm. Hg in the early sixties. Average diastolic pressures vary from 71 mm. Hg in the teens to 80 mm. Hg in the early sixties. Women, on the average, have pressures which are slightly lower than those of men below age 40, about the same as those of men in the forties, and slightly higher than those of men at ages over 50. On the basis of these studies, the traditional rule of "100 plus your age" is woefully inaccurate. A better rule of thumb for average blood pressure has been suggested by E. A. Lew, Chairman of the Mortality Committee of the Society of Actuaries at the time of the compilation of the data of the 1959 study: average systolic blood pressure = one third of age plus 111 and average diastolic blood pressure = one fifth of age plus 68.

The average systolic pressures found in the 1959 study are slightly lower than those found in the first large-scale study of blood pressures, the Blood Pressure Study, 1925,[2] and are not markedly different from average blood pressures found in large industrial populations[3] and World War II selectees.[4] Individuals with very high elevations of blood pressure are generally not included in insurance studies of mortality since they were not issued insurance. This may account for slightly lower average blood pressures in insurance studies, particularly in individuals over the age of 50. Aside from this slight variation, the broad spectrum of society represented by holders of insurance policies provides a greater cross section of the population of the United States and Canada than that found in any other large-scale study of blood pressure.

Although it has long been known that mortality increases as blood pressure rises, blood pressures at which significantly increased mortality is experienced are found to be lower in this latest mortality study than in previous studies. For example, the results of the 1959 study indicate that readings of 132/90 mm. Hg and 143/85 mm. Hg at ages under 40 years would be associated with a mortality 50 per cent greater than average mortality for that age group. Similarly, readings of 138/90 mm. Hg and 144/85 mm. Hg at ages over 40 years would be associated with a mortality 50 per cent greater than average for that age group. In order to correct a common misunderstanding of persons not familiar with mortality studies it should be pointed out that a mortality which is 50 per cent greater than average does not mean that life expectancy is reduced by half. Actually, a 50 per cent increase in mortality at age 35 would decrease the normal life expectancy by about 10 per cent; the decrease would be less than 10 per cent below the age of 35, but increasingly greater at older ages.* At any age from 20 to 70 years, as systolic blood pressure approaches 140 mm. Hg or diastolic blood pressure approaches 90 mm. Hg (even on a casual reading), mortality increases and the individual faces the possibility of significantly reduced life expectancy.

*A 50 per cent increase in mortality would have the following effect on the life expectancy of men in good health and in safe occupations: at age 20, life expectancy reduced from 55.8 years to 51.4 years, or by 7½ per cent; at age 35, life expectancy reduced from 41 years to 37 years, or by 10 per cent; at age 60, life expectancy reduced from 20 years to 17 years, or by 15 per cent.

Even when allowance is made for women's natural advantage over men in life expectancy, the mortality associated with elevated blood pressure in women is still generally lower than that in men. However, this favorable situation does not hold true below age 40; younger women do not, on the average, appear to handle elevated blood pressure better than men.[8]

The reliability of blood pressure readings found on life insurance examinations has been questioned by physicians, especially readings at levels of blood pressure at which companies begin to charge extra premiums. Also, questions have been raised in regard to the value of casual readings, which may be higher than usual. However, in the 1959 mortality study, when extra premiums were charged, two or more readings were taken on 80 per cent of the subjects and three or more readings were taken on 60 per cent of the subjects. Inference is made also that there may be a tendency for insurance examiners to diminish actual readings slightly if they are in the range of 140/90 mm. Hg. If this were true, blood pressures around 140/90 mm. Hg in an insurance study would represent somewhat higher actual pressures and show a mortality higher than they should. I do not believe that this is a valid criticism for the following reasons. First, the average blood pressures in the mortality studies compare favorably with average blood pressures found in other large-scale studies.[1,4,8] Second, insurance examiners are selected by their respective companies from the active practicing physicians in their communities. More than with their fellow practitioners, their work is subject to review and checks in the due course of underwriting procedures. Third, I had the opportunity to compare average blood pressures taken on 1,000 insurance applicants by specially selected qualified internists with the average blood pressures found in the Build and Blood Pressure Study, 1959. The distribution of the readings and the averages obtained were almost identical in the two groups. This constitutes strong evidence that blood pressures found on life insurance examinations are reliable for statistical study.

Mortality studies of this type are of value to insurance companies in establishing standards for evaluating insurance risks, whereas they are of value to the physician by indicating danger areas. They indicate where the physician should be watchful since they emphasize the threat to longevity of so-called "minor" departures from average. Large volumes of statistical data provide a means of measuring the effect on longevity of slight deviations from "good health." Clinical studies usually do not follow up the effect of slight deviations on longevity.

Insurance studies of blood pressure of the type mentioned do not measure morbidity; they are neither intended nor designed to do so. They are purely statistical and do not take into account underlying disease processes; they are reasonably homogeneous, however, because the subjects have been screened to eliminate individuals with positive urinary findings, overweight, family history of cardiovascular disease, or any other known impairment of the individual.

The practicing physician must certainly evaluate his patient by visualizing him in relation to his home, his work, and his dinner table. He may, in exercising medical judgment, disregard slight elevations of blood pressure in individual cases. However, he should bear in mind that even slightly elevated blood pressure has an adverse effect on longevity in the long run, especially if it persists.[7] This knowledge should alert him to look for underlying arteriosclerosis, renal disease, and other disease states known to produce hypertension and which may be amenable to therapy. The effect of antihypertensive drugs on mortality remains to be seen. The indications are that they have a favorable effect on morbidity associated with hypertensive disease. One potential danger which the physician frequently finds associated with slightly elevated blood pressure is overweight. For the patient who shows this combination, the doctor should prescribe a program of weight reduction and control. He will thus offer his patient a more favorable life expectancy.

REFERENCES

1. Society of Actuaries: Build and blood pressure study, Vol. 1, 1959; Vol. 2, 1960.
2. Society of Actuaries: Blood pressure study, 1925.

3 Master A M Dublin L I and Marks H H : The normal blood pressure range and its clinical implications J.A M A 143:1464 1950
4 Karpinos B D Blood pressure and its relation to height weight race and age World War II Am J Hyg 68: (N) 3) 288 1958.
5 Benford D M Review of the build and blood pressure study 1959 Proceedings of the 48th Annual Meeting of the American Life Convention 1960
6 Robinson S. C., and Brucer M : Range of normal blood pressure Arch Int Med 64:409 1939
7 Hines E. A Jr : Range of normal blood pressure and subsequent development of hypertension J.A M.A 115:271 1940

Clinical communications

Cardiovascular studies in the Samburu tribe of Northern Kenya

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Kampala Uganda

This study of the Samburu tribe of Northern Kenya has been undertaken with the purpose of assessing some of the physical and cardiovascular characteristics of a nomadic people who live on a diet of milk and meat, and who are physically very active. Relatively few studies are available concerning blood pressure and body build in similar population groups living in the tropics and subtropics there have been no studies on blood lipids or electrocardiographic patterns and no autopsy studies.

In view of the uncertainty which still exists concerning the relationship between environmental factors (e.g physical activity dietary pattern) blood lipids and coronary atherosclerosis, there is clearly a need to investigate fully the possible effects on blood lipids and on coronary heart disease of large muscle activity in persons and groups ingesting diets which in theory are potentially atherogenic.

This work has been in the nature of a pilot survey that is an attempt to assess whether more prolonged and elaborate investigations are warranted either in this particular society or in similar social groups still in existence in Africa

Socioeconomic background of the Samburu The Samburu are a nomadic Nilo-Hamitic tribe living in the Northern Province of Kenya and dependent entirely on their herds of cattle sheep and goats for their economy and livelihood agriculture is completely absent from the society

Every adult male belongs to a particular age set and the time of his initiation into that age set determines his sub-age set each of these separate groups has a specific name. The three main groupings are boys, warriors and elders, and with a detailed knowledge of this social organization it is possible to make a fairly accurate assessment of individual ages.

Physical activity At all age levels there is a fairly high degree of physical activity associated with the herding watering and grazing of cattle. Family migrations usually take place every 6 weeks or so the whole settlement moves about 10 to 15 miles whereas seasonally cattle may be driven by the younger men to areas 50 or even 100 miles distant in search of grazing or water The task of herding the main stock is undertaken by older boys, warriors, and elders, and a day's herding may involve a trek of up to 20 miles. Warriors and elders who are not herding will assist with watering cattle and this may involve lifting 400 gallons of water 4 or 5 feet by hand every other day using only a wooden bucket.

Long distances are traveled by the warriors in their wanderings around the countryside and they may walk [illegible]

From the Department of Medicine, Makerere College Medical School, Kampala, Uganda.
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or more a day in the hot sun for several days in succession. The early years of elderhood are usually harsh and exacting and as a man grows older his physically active role becomes less marked although he will spend a considerable amount of time in search of lost cattle or visiting nearby settlements or villages.

Diet. The diet consists almost entirely of milk and meat. Blood is a variable and minimal part of the diet and is used to any extent only during the dry season. Carbohydrates are practically absent from the diet of the warriors and elders and vegetables are eaten only in very small quantities. The warriors may drink some 4.5 to 7 liters of milk at a single sitting and during the wet season when milk is plentiful they will do this twice a day; the amount will diminish to a total of 2 to 3.5 liters a day or even less in the dry season. Meat may be taken infrequently when milk is abundant and once or twice a week in the dry season. The elders drink less milk than do the warriors and take meat more regularly for unlike the warriors they are under no ritual prohibitions. Semiquantitative assessments indicate a high fat high protein and low-carbohydrate diet, but there is clearly a marked seasonal variation in intake.

The average fat content of several specimens of Samburu milk examined was 5.6 per cent and allowing for daily intakes of 3.5 liters for boys and elders and of 7 liters for warriors and young elders when supplies are adequate this will give daily intakes of 196 and 392 grams of fat respectively providing at least 60 per cent of total caloric intake. In regard to the Samburu district as a whole milk is probably abundant for some 4 months of the year sufficient for needs during an additional 4 months, and insufficient during the remaining 4 months when meat has to be used to supplement the diet. Even though cattle and small stock are, in theory available to maintain food intakes during periods of inadequacy cultural patterns are such that animals are not readily slaughtered even in time of need and imported foodstuffs (e.g., maize meal) are by custom not taken by adult males. Thus, the high fat high-protein diet varies quantitatively with the seasonal variations in supply and periods of frank famine are not unknown in the Samburu territory.

Material and methods

This study was carried out in the Maralal Wamba area of the Northern Province of Kenya during April 1960. There had been an exceptionally severe dry period before our visit but slight rain had fallen in December 1959 and more rain fell in March and April 1960. The survey was restricted to males and in all 105 warriors (age range of 16 to 31 years mean age of 26 years) and 178 elders (age range of 34 to 90 years mean age of 47 years) were studied. Ages were assessed by Paul Spencer an anthropologist who had lived for over 3 years as a member of the Samburu tribe. This was done by ascertaining the age set and sub-age set of each subject and the method was considered to be accurate to within 2 years for the majority of subjects.

All subjects were weighed and their heights measured. Blood pressures were recorded by one observer[a] after the subjects had been seated for several minutes with the cuff in position. The lower of two to three readings was recorded and the diastolic pressure was read at the onset of the fourth phase. Electrocardiograms were obtained on 100 subjects (age range of 34 to 90 years mean age of 48 years) using a direct writing transistor cardiograph operated by batteries. Tracings were only recorded with the subjects at rest, and chest leads were limited to V_2, V_4 and V_6 positions. The following estimations were carried out on samples of venous blood obtained in the morning: total cholesterol (1) lipid phosphorus (2) triglycerides (3) and total fatty acids (4).

Information on diet was compiled from the personal experience of Paul Spencer and from repeated and detailed enquiries made by myself during this survey and on earlier visits to the area. No formal survey of diet has been attempted in this nomadic group but this is to be carried out in the near future by the Kenya government.

Results

The majority of the males were on the lean side the warriors were slender rather

than muscular in appearance and only a few individual elders were observed who could be considered to be overweight.

A 19-year-old male had a congenital heart disorder (probably Fallot's tetralogy) another of the same age had clinical evidence of right ventricular hypertrophy and still another one a 31 year-old warrior had early mitral incompetence with slight left ventricular hypertrophy

No clinical evidence of cardiovascular disease was noted in any of the elders examined although peripheral arteriosclerosis was not uncommon in the older subjects.

Body build and blood pressure The Samburu are predominantly lightweight individuals and with increasing age no increase in average weight is recorded. The mean height for all the males is 68.9 inches (S D 2 9 inches) and the mean weight of 126 2 pounds (S.D 14 0 pounds) remains remarkably constant in each decade of life from the third onward The average increase in weight for each inch of increase in height is 1 7 pounds this is about one third of the increase seen in American males.[5]

Comparison of American and Samburu average weights by age (with due allowance for clothing) shows a difference in mean weight at 20 to 29 years of 25 pounds this difference increases to 34 38 and 39 pounds, respectively in the subsequent three decades and falls slightly to a difference of 35 pounds in the 60 to 69-year period Almost nine tenths of the Samburu males are less than 90 per cent of American average weights for their height and age.

Data on blood pressure in adult male Samburu are given in Table I The systolic blood pressure is significantly lower than that of Americans[4] at all ages and shows no increase with increasing age from 20 to 59 years. A rise in systolic pressure is recorded in the over-60 group. Corrected for differences in method diastolic pressures in the Samburu are lower than those in Americans at all ages and fall significantly in the Samburu after the age of 49 years.

Levels of plasma lipids The mean levels and standard deviations of the four lipid components studied and the ratio of cholesterol to phospholipids (C/P) are shown by age decades in Table II When warriors and elders are compared as two separate groups no statistically significant differences can be demonstrated between the mean levels in any of these components,[6] although when grouped according to age decades as in Table II there is a statistically significant fall in the 50 to 59 group in both total cholesterol and levels of phospholipids with corresponding changes in the C/P ratio. The level of cholesterol remains lowered into the over-60 group whereas the level of phospholipids rises again in this age group

Electrocardiographic findings Electrocardiograms were obtained on 100 elders (age range of 34 to 90 years mean age of 48 years) No gross cardiovascular disease was noted in any of these elders. Only 3 subjects had an elevated diastolic blood pressure (135/95 145/100 mm. Hg) but without evidence of left ventricular hypertrophy and in these 3 subjects the electrocardiogram was normal

Possible ischemic patterns were seen in 2 subjects—one aged 32 years with slight T wave inversion in several leads and one aged 81 years with a left bundle branch block. In neither of these two subjects did the tracings show conclusive evidence of myocardial disease. Moderate flattening of T waves without inversion or other significant changes were noted in 7 other subjects.

Discussion

Is the rise in systolic and diastolic pressures seen in so many populations a normal phenomenon or is it a reflection of

Table I Blood pressure by age in adult male Samburu. Mean systolic and diastolic levels and standard deviations

Age decades	Number	Systolic	S.D	Diastolic*	S.D
20–29	41	111 5	10 8	76 5	7 0
30–39	79	112 3	12 3	76 7	8 1
40–49	54	112 2	14 1	78 8	8 1
50–59	43	109 2	10 3	74 9	7 6
60+	22	116 6	14 1	74 8	7 2

*Diastolic readings recorded as fourth phase.

Table II. Plasma lipids in adult Samburu males (in milligrams per 100 ml. with mean values and standard deviations)

	Age decades						*Total*
	15-19	*20-29*	*30-39*	*40-49*	*50-59*	*60+*	
Number of subjects	13	[illegible]	[illegible]	33	27	10	201
Total cholesterol							
Mean	164.0	[illegible]	170.0	165.0	151.0	144.0	[illegible]
S.D.	42.6	39.4	35.5	37.9	34.0	38.1	39.2
Phospholipids							
Mean	[illegible]	[illegible]	214.5	226.1	193.0	223.4	212.0
S.D.	[illegible]	[illegible]	33.3	[illegible]	[illegible]	12.8	34.5
C/P ratio							
Mean	[illegible]	0.83	0.80	0.74	[illegible]	0.69	[illegible]
S.D.	0.15	[illegible]	0.11	0.15	0.12	0.12	0.14
Total fatty acids							
Mean	243	[illegible]	[illegible]	[illegible]	244	242	254
S.D.	[illegible]	60.4	[illegible]	45.3	41.9	44.9	[illegible]
Triglycerides							
Mean	[illegible]	83.5	[illegible]	83.5	84.0	[illegible]	85.0
S.D.	[illegible]	49.4	[illegible]	[illegible]	[illegible]	41.9	31.9

the incidence of hypertension in the communities observed.[3] Studies within East Africa[4] indicate that although large increases in blood pressure with age are unusual, significant variations in mean levels of blood pressure and in the relationship of blood pressure to age may occur from one tribal and geographic area to another whereas a study in West Africa has indicated a close parallel between American and African patterns of blood pressure.[5]

In a recent review of blood pressure in relation to age and sex in the tropics and subtropics, Lowenstein[6] discusses some 26 references concerned with various ethnic and social groups. He considers that those of the groups reviewed which show no increase in mean blood pressure with age during adult life represent relatively small homogeneous populations living under primitive conditions, more or less undisturbed by their contacts with civilization. The rise in blood pressure seen with age in most of the groups he reviews is, in his opinion, "a consequence of civilization or the process of acculturation." From a study of Bushmen in the Kalahari, Kaminer and Lutz[7] also conclude that a rise in blood pressure is not a characteristic of a normal aging process and regard it as an indication of the existence of essential hypertension in a community.

Our findings in the Samburu would suggest that an increase in weight and a rising blood pressure are not necessary accompaniments of the aging process. The rise in systolic blood pressure seen in the seventh decade in the Samburu is not due to the presence of hypertension in this group and may be a manifestation of decreased elasticity of the aorta and larger blood vessels.

The mean level of plasma cholesterol for all Samburu males is comparable to that found, by an earlier study, in healthy adult African males of Kampala, Uganda, who were living on a diet to which fat contributed 10 to 15 per cent of the total calories.[11] More recent investigations into dietary patterns and blood lipids have shown that the customary dietary habits of communities are usually reflected in their mean levels of serum cholesterol, and that increases in the consumption of

animal fat lead to approximately parallel increases in the mean levels of blood cholesterol. In the light of the dietary pattern described in the Samburu tribe their levels of cholesterol seem to be contrary to this thesis and require explanation. The mean levels of phospholipids, total fatty acids, and triglycerides are also in keeping with levels found in groups on lower fat diets.[5]

Initially an attempt must be made to answer the question whether differences in habitual physical activity could account for the variations in the concentrations of blood lipids in different populations, and in particular whether this factor might be responsible for the unexpectedly low levels of lipids in the Samburu. Reviewing at length the data from many countries, Keys[12] concludes that physical activity does not explain the *large* differences in concentrations of serum cholesterol observed between populations eating different amounts of fat. This is not to deny the possibility that physical exercise plays some part in regulating the concentration of lipids in the blood but it does not appear to be a major regulating mechanism.

It seems reasonable to suggest that the low levels of blood lipids found in the male Samburu are in the main associated with the quantitative variability in their high-fat diet and that their high degree of dynamic physical activity does not by itself account for these findings. The findings on blood lipids in the Samburu would suggest that for a high intake of butter fats or other saturated fats to produce abnormally high levels of lipids in the blood the intake must be habitual and probably must be part of a lifespan pattern of diet.

Although the number of Samburu studied by electrocardiography is far too small to allow any conclusive statement to be made concerning the relative frequency of the complication of coronary heart disease there is at present no autopsy information available from this tribe. All we can suggest at the time of writing is that the complications of coronary atherosclerosis, as evidenced by our electrocardiographic findings are apparently uncommon in the adult male Samburu. Even though minor changes suggestive of ischemia are noted it must be remembered that in some parts of Africa there is convincing evidence that electrocardiographic changes which in Europe would be interpreted as indicating ischemic heart disease may be found in a large proportion of healthy subjects.[8,14] It is clearly undesirable to rely solely on this relatively small electrocardiographic survey and supporting pathologic information is being sought.

By the accumulation of data concerning peoples who live in special environmental situations and at different levels of civilization studies in geographic pathology such as the present one may lead to a better understanding of some of our cardiovascular problems e.g. essential hypertension and coronary atherosclerosis. Although the urgent requirement is for adequate autopsy material which can be correlated with clinical and biochemical information, this is seldom if ever available in areas such as we have described and by the time that adequate pathologic facilities are available it may well be that the way of life has been significantly altered as regards dietary habits and patterns of physical activity.

It must be emphasized that this has been an uncontrolled pilot study. In order that more definite conclusions may be reached seasonal studies as well as individual absorption studies are now being carried out and direct comparisons are being made with other groups in East Africa. The results of these more extensive studies will be reported later.

Summary

The Samburu tribe of Northern Kenya live on a diet of milk and meat and are physically very active. There is no increase in weight with age, and only a small increase in weight with advance in height. They show no rise in systolic blood pressure until the seventh decade and diastolic pressures fall after the fifth decade. Levels of lipids in the blood are comparable with those found in groups living on low fat diets, and it is suggested that this phenomenon is related to the seasonal variation in supply. Initial electrocardiographic studies suggest a low incidence of coronary heart disease. Further studies are in progress to investigate more fully the many questions raised by this initial survey.

The members of this expedition included Professor A. W. Williams, Dr P G Wright, Mr J Kyobe, and Mr P Spencer Without their energetic participation this work would not have been possible. We wish to thank the District Commissioner Samburu District, for permission to conduct this survey in the Maralal-Wamba area, and the Department of Physiology for the use of their mobile laboratory (Wellcome Trust).

REFERENCES

1 Abell, L. L., Levy B B Brodie B B and Kendall, F E. A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity J Biol. Chem 195:357 1952.
2. Bartlett, G R. Phosphorus assay in column chromatography Modification of Fiske and Subba Row method J Biol. Chem. 234:466, 1959
3. Van Handel E., and Zilversmit, D. B Micromethod for determination of serum triglycerides, J Lab. & Clin. Med. 50 152, 1957
4 Stern, I and Shapiro, B : A rapid and simple method for the determination of esterified fatty acids and for total fatty acids in blood, J Clin Path 6 158, 1953
5 Shaper A. G., Williams, A. W and Spencer P Blood pressure and body build in an African tribe living on a diet of milk and meat, East African M J 1962 (In press)
6. Shaper A. G Jones, M and Kyobe, J Plasma lipids in an African tribe living on a diet of milk and meat, Lancet 2:1324, 1961.
7 Williams, A. W To be published.
8. Abrahams, D G Alele, C. A., and Barnard B G The systemic blood-pressure in a rural West African community West African M J 9:45 1960
9 Lowenstein, F W Blood pressure in relation to age and sex in the tropics and subtropics, Lancet 1:389 1961
10 Kaminer B and Lutz, W P W Blood pressure in Bushmen in the Kalahari desert, Circulation 22:289 1960
11 Shaper A. G and Jones, K. W Serum cholesterol, diet and coronary heart disease in Africans and Asians in Uganda, Lancet 2:534, 1959
12. Keys A. Diet and the epidemiology of coronary heart disease, J.A.M.A. 164 1912 1957
13 Grusin, H : Peculiarities of the African's electrocardiogram and the changes observed in serial studies, Circulation 9:860, 1954
14 Powell, S. J : Unexplained electrocardiograms in the African, Brit. Heart J 21:263, 1959

Suprasternal puncture of the left atrium and the great vessels Experience from 500 punctures

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The suprasternal puncture of Radner (1955) has been employed routinely in our laboratories to obtain pulmonary arterial and left atrial pressures, particularly in cases of mitral valvular disease. The principle of the method is shown in Fig. 1. A very thin needle is used in order to keep hemorrhage to a minimum. The needle is inserted from the fossa jugularis and directed downward and forward between the manubrium sterni and the trachea. The aorta is punctured first, then the pulmonary artery, and finally the left atrium. The punctures are carried out under continuous recordings of the pressure so that the course of the puncture can be monitored on the basis of the curves which are observed on an oscilloscope. Radner and associates[1] published their experience with 140 successful punctures of this kind without complications, and in the following report we shall present our observations in 500 subjects who have been punctured one or more times. The suprasternal puncture has been performed in another 149 patients simultaneously with a percutaneous puncture of the left ventricle from the front of the thorax. These combined punctures have been reported upon elsewhere (A. Tybjaerg Hansen et al., 1961).

Technique

The assembled apparatus is shown in Fig. 2. The needle employed is 20 cm. long, its outer diameter is 0.8 mm., and its inner diameter is 0.4 mm. In order to support the highly flexible needle during the puncture a guidance device is used. It consists of a metal tube, 2 cm. long, which is fixed on a shield. The needle is connected with a capacitance manometer[1] by means of a transparent nylon tube which is 50 cm. long and has an inner diameter of 0.8 mm. A 2-c.c. syringe is attached to it by means of a three-way stopcock between the manometer and

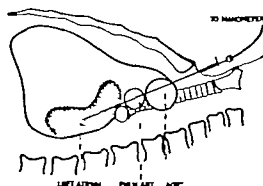


Fig. 1. Schematic diagram which illustrates the principle of the suprasternal puncture.

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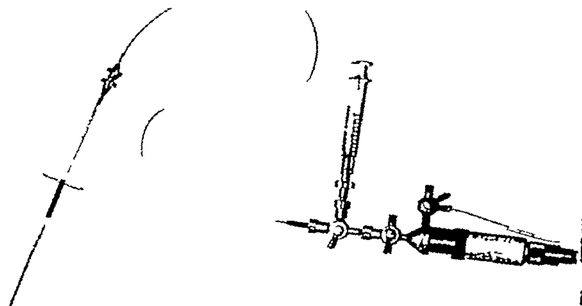


Fig. The apparatus assembled. *Seen from the left*, needle with guiding device, nylon catheter syringe, and manometer

he nylon tube. In order to ensure complete air free filling of the entire pressure transmitting system the single parts are boiled separately and completely submerged in water. After being boiled the parts are screwed together without being taken out of the water. If a change of needle becomes necessary great care must be taken to prevent air from replacing liquid in the needle by keeping it in a horizontal position and to flush the nylon tube continuously with a saline solution while the needle is being screwed on to its connecting piece. The midaxillary line of the patient is used as zero reference and as a second reference pressure a liquid column corresponding to 30 mm. Hg. The pressure curve and the electrocardiogram are visualized on an oscilloscope and are simultaneously recorded photographically. The natural damped frequency of manometer plus nylon tubing and needle has been experimentally determined to be 45 to 50 cycles per second.

Procedure

Before the puncture is made the bleeding time and the coagulation time are checked and must be found to be normal. Two hours before the puncture is to be made 200 mg. of phenobarbital is given perorally. Only local anesthesia is used in adults. In children who are under 5 years of age a complete anesthesia may be preferable. The local anesthesia (xylocaine 1 per cent with norepinephrine) is applied cutaneously and subcutaneously in the fossa jugularis.

The examination is carried out with the patient in a supine position. His shoulders are lifted by means of a cushion. His head should be turned slightly backward and the face to the left. In order to facilitate the introduction of the point of the needle the skin is perforated with a small sharp knife in the median plane about 1.5 cm. cranad from the upper edge of the manubrium. During the puncture the needle is kept exactly in the sagittal plane and is pushed downward and forward between the manubrium sterni and the trachea. The inclination of the needle has to be changed slightly from one patient to another but as a rule it will prove suitable to choose a direction which forms an angle of 30 to 40 degrees with the horizontal

plane. In individual cases an estimate of the optimum direction may be obtained from a radiogram of the thorax in the sagittal plane.

The course of the puncture is checked as mentioned earlier by observing the typical pressure curves on the oscilloscope. In addition the operator will generally recognize rather distinctly when the point of the needle touches the pulsating wall of the aorta and when it perforates the tough wall of the left atrium. If the needle is introduced too vertically the operator will feel that the point hits the tough and hard tracheal cartilage. If the puncture is pressed on a cough will be provoked which sometimes will be accompanied by slightly blood tinged expectoration.

If the pressure curves desired are not obtained by the first direction chosen for the puncture the attempt is repeated with a different inclination of the needle Only rarely does it become necessary to introduce the needle through a fresh incision in the skin a little closer to or more distant from the upper edge of the manubrium

In the course of the puncture it is possible to take out small samples of blood—1 to 2 ml —for determination of oxygen saturation Likewise it is possible to inject a dye through the needle in order to determine the cardiac output according to the Stewart Henriques-Hamilton principle It is our experience that there is time enough for such procedures, since it seems that the needle can be kept in the same position for at least 10 to 15 minutes without any risk once the tip of the needle lies clear in one of the great vessels or in the left atrium If the pressure curves are being damped during the examination the needle is flushed with a 0 9 per cent saline solution from the syringe

Material

The average age of the patients was 39 years. The majority were between 25 and 50 years of age 6 were over 60 years, and only 4 were under 14 years. Symptoms of rheumatic valvular disorders were found in 485 patients. Of these 442 had a predominant mitral disease and 43 had aortic valvular disease. The other 15 patients showed various lesions and abnormalities and in these patients the puncture was carried out either to exclude the possibility of a silent mitral stenosis or to find out whether the conditions were complicated by pulmonary hypertension.

As might be expected pressure curves from the aorta the pulmonary artery and the left atrium constituted the usual sequence. Quite often however the pulmonary artery was punctured without a preceding puncture of the aorta and in some cases the needle slipped behind both of the great vessels, so that only the left atrium was punctured In 30 patients the left ventricle was punctured and in another 3 patients a pressure from the right ventricle was registered. The puncture of the two chambers did not lead to any complications.

The curve from the left ventricle was usually obtained immediately after the curve from the aorta but in a few cases it followed the curve from the left atrium. In such instances the point of the needle probably had entered the left ventricle by way of the aortic and the mitral ostium respectively

The results from the entire material show that the left atrium was punctured in 73 per cent of the examinations, the arteria pulmonalis in 68 per cent and the aorta in 71 per cent of the cases. If the latest 200 punctures are taken separately the number of successes is essentially higher 90 80 and 76 per cent respectively This is partly a result of sheer practice and partly a consequence of less hesitancy toward repeated attempts to puncture a particular cavity in order to obtain a desired pressure This attitude of course has developed as the accumulated experience indicated that the punctures were accompanied by but little discomfort on the part of the patient and by very few and minor complications.

The relatively high percentage of successful punctures of the left atrium is due to the preponderance of cases of mitral disease in which the left atrial pressure at the same time is so important and so relatively easy to obtain because of the enlargement of the left atrium in these cases.

The pressure curves obtained were technically satisfactory in almost all cases. Fig 3 shows typical sets of curves.

The duration of the complete procedure

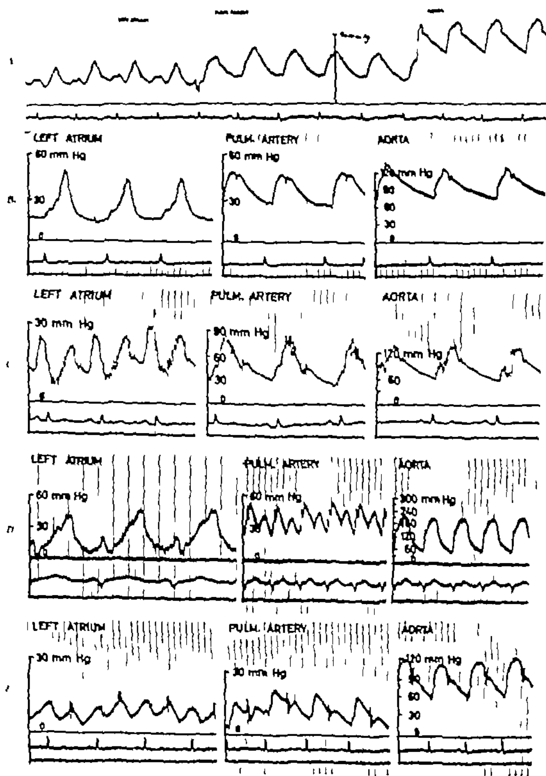


Fig. 3. Some examples of pressure curves. In *A* the curve is recorded during the withdrawal of the needle from the left atrium to the pulmonary artery and the aorta. The recordings of the pressure in the three structures are given here with the same amplification. In the other examples the amplification used in the recording of the pressure of the left atrium and the pulmonary artery was higher than that used for the aorta, in order to obtain the best representation of details. The curves in *E* were taken from a patient without organic heart disease. *A*, Mitral stenosis in a 25-year-old woman. *B*, Mitral incompetence in a 31-year-old woman. *C*, Aortic stenosis and incompetence in a 50-year-old man. *D*, Aortic and mitral incompetence in a 49-year-old woman. *E*, Cardiac neurosis in a 25-year-old woman.

was normally 10 to 15 minutes and in most cases it was possible to examine several patients in rapid succession since only the needle had to be changed from one patient to another. In comparison catheterization of the right side of the heart with measurement of the pulmonary arterial and the pulmonary arterial wedged pressures, cannot usually be carried out in less than 1 hour and the preparations for this examination are much more elaborate.

In order to evaluate the results of the suprasternal puncture technique as compared with catheterization of the right side of the heart we have measured the pressures obtained by both methods simultaneously in 13 patients. The pulmonary pressures were recorded concurrently in all patients, and in 9 patients the wedged pressure and the pressure in the left atrium were also measured. As expected no significant difference was found between the pressures of the pulmonary artery measured by the two methods. Also the shape and the height of the pressure curves of the left atrium and the wedged pressure agreed on the whole (Fig. 4).

In an additional 56 patients, catheterization of the right side of the heart and a suprasternal puncture were made within an interval of less than a month. In 45 of these patients the pressure in the pulmonary artery was recorded by means of both methods of examination and in all 56 patients determinations of wedged pressure and left atrial pressure were made. By and large the accordance between the results was satisfactory (see Figs. 5 and 6).

In the more recent punctures the recording of the pressures has been supplemented more routinely with a determination of the cardiac output. Dye was injected into the left atrium through the needle and arterial blood was sampled from a catheter inserted into the femoral artery. In most cases well formed dye-dilution curves with a very steep slope were obtained.

Complications

The complications in 500 suprasternal punctures are listed in Table I. There were no fatalities. Only 1 patient developed alarming symptoms of pneumothorax. He was a 51 year-old man who was suffering from bronchial asthma and chronic bronchitis, with resting dyspnea and slight cyanosis. The vital capacity was 2.5 liters, maximum breathing capacity 26 liters per minute, arterial oxygen saturation 82 per cent, pCO_2 55 mm. Hg and pH 7.5.

The suprasternal puncture which was aimed primarily at obtaining information about the pulmonary arterial pressure was

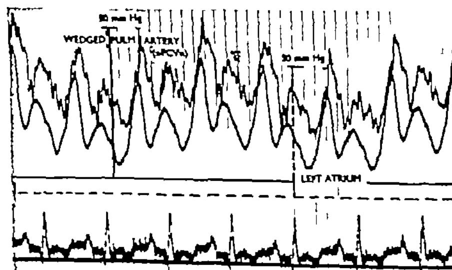


Fig. 4. Pressure curves from the left atrium and the pulmonary capillary recorded simultaneously. Note the base lines.

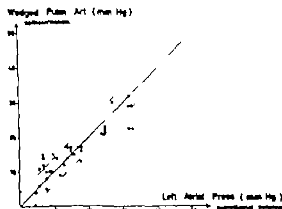


Fig. 5. The relation between the pressure in the pulmonary capillary and the pressure in the left atrium in nonsimultaneous recordings in 56 patients. The dotted lines limit the field ±4 mm. Hg. The two recordings in each patient were made with an interval of 1 to 4 weeks.

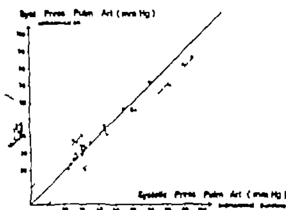


Fig. 6. The relation between pulmonary arterial pressures recorded nonsimultaneously by suprasternal puncture and catheterization of the right side of the heart in 56 patients. The dotted lines limit the field ±10 mm. Hg. The two recordings in each patient were made with an interval of 1 to 4 weeks.

carried out uneventfully. The pulmonary arterial pressure was slightly elevated (55/29 mm. Hg) with normal aortic pressures and left atrial pressures. During the following 2 hours he complained of slightly increased dyspnea. An x-ray photograph showed a hood-shaped pneumothorax on the left side about 0.5 cm. wide. One hour later the symptoms suddenly became much worse in accordance with an increase in the pneumothorax to 3 cm. Pleural puncture was performed and permanent suction was instituted, after which the symptoms vanished and complete recovery was obtained within a week.

This case undoubtedly is representative of the type of patient who more than anybody else is liable to develop serious symptoms in connection with a suprasternal puncture. The emphysematous lungs will very easily get in the way of the needle and because they are also more vulnerable, pneumothorax presumably will develop more often and, in addition, give rise to much more serious symptoms in these patients with poor function of the lungs than it does in persons who are normal in this respect. The case also serves to emphasize the importance of early and repeated x-ray control of the thorax if symptoms develop.

In the other patients the complications were few and rather innocent. During the first hours after the puncture most of them experienced a slight pressure behind the sternum, but it was necessary to give analgetics in only 3 cases. The trachea was hit several times and in a few patients this resulted in a blood-tinged expectoration, but otherwise it caused no inconveniences. During and immediately after the puncture 7 cases of nausea, perspiration, pallor, and drop of systolic blood pressure to 60 to 80 mm. Hg developed. The symptoms disappeared within a few minutes in all patients, spontaneously in 6 of them and after an intravenous injection of 1 mg. of atropine in the seventh. Pulmonary edema also occurred during puncture in one pa-

Table I. Complications in 500 suprasternal punctures

Type of complication	*Number of cases*
Pneumothorax with excessive cyanosis and loss of consciousness	1
Pneumothorax without clinical symptoms (x-ray)	1
Slight drop in blood pressure, bradycardia, nausea, and pallor	7
Pulmonary infarction	1
Transitory paresis of left hand	1
Pulmonary edema	1
Small mediastinal hematoma (x-ray)	16
Small pericardial hemorrhage (observed at operation)	20

tient with a severe mitral stenosis who had had repeated attacks of pulmonary edema earlier. The attack disappeared after an injection of morphine. During the first couple of days after the puncture, 2 patients showed symptoms which might have been of thromboembolic origin. One patient had a transitory difficulty in directing the *left* hand; this lasted for 1 hour. A 14-year-old boy who had been cardially decompensated for a long time because of myocarditis of unknown etiology developed during the first 48 hours after the puncture symptoms of lung infarction with a rise in temperature and pains in the right half of the thorax. X-ray examination of the thorax showed a wedge-shaped infiltration in the right lung. The patient was treated with anticoagulant and penicillin and the symptoms subsided after a few days. The rest of the complications were unaccompanied by clinical symptoms and signs. X-ray photography of the thorax which was performed routinely after the puncture before the patients were returned to the ward revealed another hood-shaped pneumothorax besides the one which was followed by serious symptoms. It vanished spontaneously within 3 days.

In 16 patients the width of the superior mediastinal shadow was increased 2 cm. or less but became normal within a week. One hundred of the patients underwent mitral valvulotomy less than a month after the puncture, and in 20 of them a blood-stained liquid was found in the pericardium. In all cases the quantity of liquid was quite small and no radiologic or other symptoms had ever been discernible.

All patients were kept in bed and had their pulse and blood pressure checked during the first 8 hours after the puncture and in no case—apart from those specifically mentioned above—was any significant decrease in the blood pressure or increase in the pulse observed within this period.

Discussion

We have modified Radner's technique in only few and unessential points. The introduction of the thin and flexible needle has been facilitated by the use of a small "leader" and the natural frequency of the pressure-transmitting system has been increased by using a thin nylon catheter as a connection between the needle and the manometer instead of a Cournand catheter as used by Radner.[3] By means of said measure we have succeeded in making the equipment more convenient to use.

Because of its nature, the suprasternal puncture is not applicable to patients who have a tendency to bleed. Since it carries a certain risk of pneumothorax, it should be used only with great caution in patients with emphysema or probably not at all in patients who have a considerably reduced function of the lungs. With these reservations the risk of serious complications seems to be slight. The frequent minor bleedings which were observed in the superior mediastinum, as inferred from the x-ray picture, and in the pericardium were functionally without importance and the brief attacks of pallor, perspiration, nausea, bradycardia, and drop in blood pressure seemed to be rather benign phenomena. As judged by the symptomatology they were of vasovagal origin, very much like the incidents observed in connection with punctures of the peripheral arteries which we have quite often witnessed. It has always been possible to bring such symptoms to an instantaneous cessation by means of an intravenous injection of atropine. Whether the few thromboembolic incidents which were observed during the first days after the procedure were much in excess of the spontaneous number expected in the kind of patients in question is doubtful. The suprasternal puncture is a technique which has its own virtues and defects, but it covers a field in which it is partly interchangeable with and partly supplementary to cardiac catheterization so that a comparison comes quite naturally.

With practice the number of successfully performed examinations approaches what one can expect from cardiac catheterization. As we have seen, the risk is hardly any higher. The short time that is sufficient for a complete examination is a definite asset for the patient, and it enables the laboratory to examine diagnostically a series of patients in rapid succession with much fewer preparations than are required for cardiac catheterization.

The technique secures much better pressure curves from the pulmonary artery

and especially from the left atrium than the estimate obtained by catheterization of the right side of the heart. The diagnostic value hereof in mitral disease is notable. Moreover, the aortic pressure curve provides information which is often of value in cases of acquired heart disease *but which is not forthcoming from catheterization of the right side of the heart.* Cardiac output is best determined by a dilution method although the Fick method can be used.

Finally, it should be pointed out that the examination is carried out without the use of x-ray fluoroscopy, which makes it particularly suited in cases of pregnant patients.

In contrast to catheterization of the *right side of the heart,* the suprasternal puncture does not ordinarily permit recording *of* right atrial pressure and right ventricular pressure. Neither does it allow measurement of pulmonary arterial pressure during exercise, which is a limitation of the method which in all other respects is so favorably applicable to the diagnostic evaluation of mitral lesions.

Summary and conclusion

The *suprasternal puncture is a* technically easy method for the determination of the pressures in the aorta, the pulmonary artery, and the left atrium.

Cardiac output can be determined by dye-dilution or isotope-dilution methods.

The risk involved is very limited as judged from our examination of 500 consecutive patients.

It is particularly valuable *in* cases of acquired heart disease with a mitral component, and more so in pregnant patients because x-ray fluoroscopy is not used.

The suprasternal puncture should not be applied to patients who have a tendency to bleed or to patients with emphysema, especially when the function of the lungs is poor.

REFERENCES

1. Hansen, A. T.: Pressure measurement in the human organism, Thesis, Copenhagen, 1949.
2. Hansen, A. T., Hansen, P. F., Sandøe, E., and Winkler, K.: Percutaneous diagnostic punctures of the heart and great vessels, Acta med. scandinav. 169:273, 1960.
3. Radner, S.: Extended suprasternal puncture technique, Acta med. scandinav. 151:223, 1955.
4. Radner, S., Linder, E., Dahlback, O., Edler, I., and Gustafson, A.: Suprasternal pressure curves in early mitral stenosis, Acta med. scandinav. 154:299, 1956.

Electrocardiographic abnormalities in cerebral disorders Report of six cases and review of the literature

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The fact that striking abnormalities in the electrocardiogram may be associated with acute cerebral disorders is not widely appreciated This article is a report on 6 patients in whom such electrocardiographic alterations occurred and for whom detailed laboratory data were available.

After the report of Levine[1] in 1953 the publication in 1954 by Burch Meyers and Abildskov[2] on an electrocardiographic pattern observed in patients with cerebral vascular accidents, and the communication by Wasserman and associates[3] on the same subject in 1956 no further detailed data appeared in American publications until 1960 when Cropp and Manning[4] reported on electrocardiographic changes in intra cranial hemorrhage. Recently a similar communication appeared in the British literature.[5] In addition a number of investigations have been published in Italy and Russia[6-8] describing electrocardiographic abnormalities in patients with cerebral vascular accidents and tumors of the central nervous system, and in patients operated upon for cerebral disorders. Furthermore, a limited number of experimental studies[4,9,10] indicate a distinct relationship between the central nervous system and cardiac electrical activity not only in regard to the development of abnormalities in repolarization but also in relation to the production of arrhythmias.

The chief phenomena to be discussed in this report consist of marked prolongation of the Q-T interval[11,12] and extremely wide deeply inverted T waves, as well as prominent U waves. They were not related to measurable electrolyte changes in the extracellular fluid Although these alterations can be observed in coronary artery disease they were unassociated with other changes indicative of recent myocardial infarction Nevertheless it should be pointed out that coronary artery disease could not be ruled out in most of our patients.

Over the course of 1 year 9 patients with such electrocardiograms were observed. Six patients in whom detailed records are available will be reported upon Three of these are women and 3 are men. In one, postmortem examination was performed In all cases the clinical record was analyzed and a careful review was made of serial electrocardiograms, electrolyte determinations and whenever possible, vectorcardiographic tracings.

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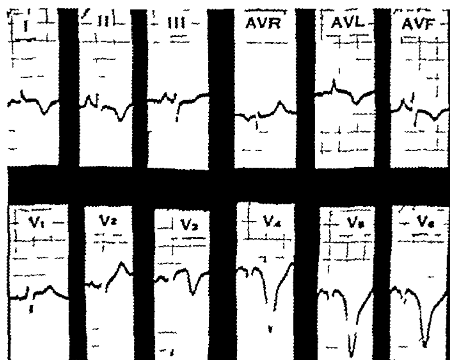


Fig. 1. Case 1. E. S., a 60-year-old woman. ECG 2 days after subarachnoid hemorrhage [illegible]. No electrolyte disturbances were present. Autopsy showed no evidence of myocardial infarction. The electrocardiographic alterations which were present 6 days prior to death are considered to be of cerebral origin.

Case reports

Case 1 E.M., PBBH 94645 was a 69-year-old housewife in excellent health until 2 hours before admission to the hospital, when she collapsed and was found comatose in her home. Physical examination showed a blood pressure of 158/100 mm. Hg and a pulse rate of 90 per minute. Cardiac examination gave normal findings. Spastic paralysis was present on the right side and flaccid paralysis on the left side of the body. There were fresh flame-shaped hemorrhages in both fundi. Laboratory tests, including electrolyte determinations, were within normal limits. The cerebrospinal fluid was loaded with red blood cells. An electrocardiogram, obtained on the second day of her illness, showed prolongation of the Q-T interval (0.40 second during a heart rate of 105 per minute) and deeply inverted, wide T waves (Fig. 1). Her clinical status did not improve, and she died on the eighth hospital day.

Pertinent autopsy data revealed rupture of a congenital aneurysm of the left internal carotid artery with massive subarachnoid hemorrhage into the left sylvian fissure, which extended from the base to the surface of the left hemisphere. The hemorrhage covered the parietal, temporal, and frontal lobes. Although softening of the temporal pole was present, no intracerebral hemorrhage was found on routine serial sections performed after fixation of the brain. Section of the pons revealed a small focus of hemorrhage and degeneration. The heart weighed 380 grams. The ostia of the coronary artery were found to be widely patent. The right coronary artery which supplied most of the posterior wall was filled distally by fresh, red jelly-like clot. The left anterior descending artery was widely patent and supplied all of the anterolateral wall. The walls of the arteries were thin and pliable, and on microscopic examination showed only minimal fibrous thickening of the intima. No atheromatous changes were present. The aorta and cerebral vessels were similarly free of atherosclerosis. The myocardium was normal except for slight hemorrhagic changes in the right lateral aspect of the apex on gross examination. Microscopic examination of this area showed dilated and engorged vessels, but no cellular infiltration or degeneration of the muscle was found, nor were these present in any of the other sections. Reviewing these findings, several pathologists agreed that no evidence for acute or subacute myocardial infarction was present.

Case 2 J. H., BCH #1091721 was a 64-year-old man who complained of loss of weight and increasing cough which proved t be due to bronchogenic carcinoma. On physical examination the blood pressure was 185/100 mm. Hg and the pulse rate was 72 per minute. The heart was slightly enlarged to the left. There was mild facial weakness on the left side; neurological function was otherwise normal. A routine electrocardiogram showed auricular fibrillation and digitalis effect (Fig. 2,*A*). Since the tumor was considered to be inoperable, the patient was treated by radiation therapy. Six weeks after admission, while he was ambulatory and comfortable, a second routine electrocardiogram showed dramatic changes (Fig. 2,*B*) which consisted mainly of a prolonged Q-T interval and deeply inverted asymmetrical T waves across the precordium as well as in the standard and unipolar leads. A vectorcardiogram obtained on the same day failed to show any evidence of myocardial infarction in the QRSsE loop. It did demonstrate a markedly abnormal T loop with a wide ventricular gradient (Fig. 3). Because of these unexpected electrocardiographic changes, electrolyte studies were repeated; these gave normal findings (Table I).

Two days after the changes noted in the electrocardiogram the patient became suddenly unconscious and developed tremor of the right leg, deviation of the head to the right, with paralysis of both upper extremities and of the right lower extremity, and responded to painful stimuli on the left side only. Hyperreflexia and a positive Babinski reflex were found on the right side. The eyes and tongue were deviated to the right, and the gag reflex was absent.

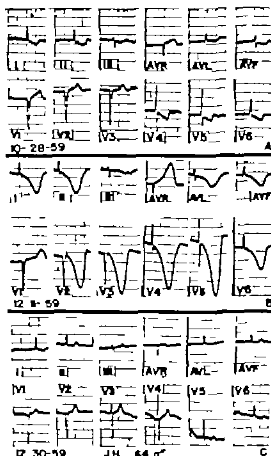
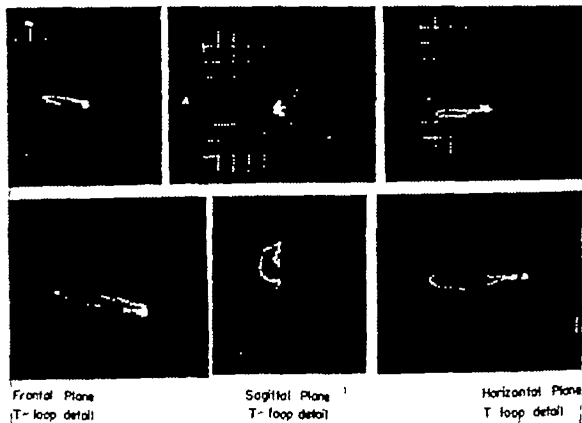


Fig. 2. Case 2. J. H., 64-year-old man with metastatic bronchogenic carcinoma. *A*, Routine electrocardiogram on Oct. 28, 1959 shows auricular fibrillation and S-T-segment depression due to digitalis effect. *B*, Tracing on Dec. 11, 1959, 2 days prior to onset of neurological symptoms and in the presence of normal serum electrolytes. *C*, Electrocardiogram on Dec. 30, 1959, 2 days before death. Peaking of the terminal T wave, which is seen best in Lead V4, may be related to the sharply elev ed level of serum potassium present on the day of death.



3 Case 2 J H Vectorcardiogram (Frank system) on Dec. 11 1959 shows abnormal, elongated T loops with maximum axis opposite to the maximum QRS axis. The frontal, sagittal, and horizontal plane loops are within normal limits, with the exception of increased terminal rightward and superior forces.

There was now a left central facial paralysis. No significant abnormality was found in the spinal fluid except for a rising total protein content, from 23 to 55 mg per cent Repeated examination of the cardiovascular system failed to reveal any abnormality other than a blood pressure of 185/100 mm. Hg

Gradual improvement occurred during the following days, until the fifth day when clonic seizures on the right side were observed these included the eyes. The seizures in subsequent days became more frequent and originated apparently from the same focus Only slight response to Mysoline was observed. The patient died 20 days after the onset of the neurological symptoms. Permission for post mortem examination was not granted.

Although the initial opinion of the neurological consultant was that an embolus was responsible for the right hemiparesis with sensory defect, the onset of focal seizures, as well as the gradual rise in total protein in the spinal fluid, indicated later that a metastatic lesion in the cerebrum was the most likely possibility

In view of the normal QRS-T loop on the vectorcardiogram as well as the improvement in the final electrocardiogram (Fig 2,C) 2 days prior to death myocardial infarction appears most unlikely It is of interest to note that this last tracing showed some T-wave peaking. Preterminally the serum potassium rose to 9 0 mEq. (Table I). However there were no significant changes in electrolytes during the period in which the electrocardiogram showed the deeply inverted T waves. The electrocardiographic diagnosis of an intracerebral disorder which preceded the neurological changes appeared to be confirmed by the sequence of events which occurred 2 days later Certainly metastatic cerebral carcinoma is the most likely cause.

Case 3. M.L., BCH #1701306, was a 57-year-old woman with known mitral valve disease. Her chief complaint was shortness of breath She also had some weakness in the right arm after an embolus to the left middle cerebral artery 6 months earlier she had recovered gradually from the latter The electrocardiogram showed auricular fibrillation right axis deviation, and biventricular enlargement (Fig. 4,A).

On the afternoon of admission to the hospital the patient complained of sudden loss of sensation and, now complete inability to move the right arm. Similar changes also occurred in the right lower extremity which had never been involved before. A second electrocardiogram was obtained and now showed sharply inverted T waves associated with slight prolongation of the Q-T interval across the precordium A tracing 2 days later demonstrated even more extensive changes (Fig 4,B). Electrolyte determinations made at this time were normal

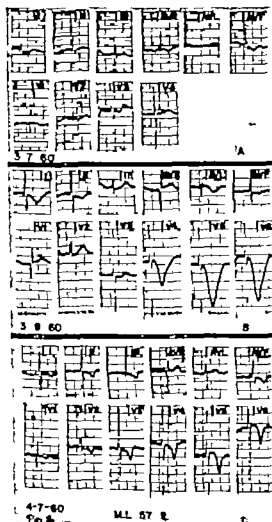


Fig. 4. Case 3. M.L., 57-year-old woman with rheumatic heart disease and cerebral embolism. A. Tracing taken on March 7, 1960, the day of admission (Leads V and V are missing). B. Tracing taken on March 9, 1960, 2 days after the onset of neurological symptoms; serum electrolytes were all within normal limits at this time. C. Electrocardiogram obtained on April 7, 1960, still shows T wave abnormalities.

(Table II). A vectorcardiogram obtained shortly afterward gave no evidence of infarction. Neurological function was recovered over the following 2 weeks. Over the same period of time the electrocardiographic changes subsided gradually (Fig. 4 C).

Case 4. C.D., LSH 63-88, a 71-year-old man was admitted to another hospital with aphasia and a complete paralysis of the left arm and left leg. He had been in excellent health until the morning of admission, when he was found unconscious in his home. Physical examination revealed auricular fibrillation, a blood pressure of 190/95 mm. Hg, and slight cardiomegaly. The diagnosis of an embolus t the right internal carotid or right middle cerebral artery was made. He was treated with large amounts of digitalis, after which normal sinus rhythm returned. The electrocardiogram at the time he was hospitalized showed an inferior myocardial infarction, without the changes usually associated with an acute process but with marked ventricular irritability (Fig. 5,A). The latter was ascribed to an excess of digitalis. There was prolongation of the Q-T interval to 0.52 second with a heart rate of 65 per minute. Over the following days, further increase in the Q-T interval occurred and deep inversion of the T waves was found (Fig. 5,B and C). The electrolyte determinations made during those days were normal (Table III). The patient was

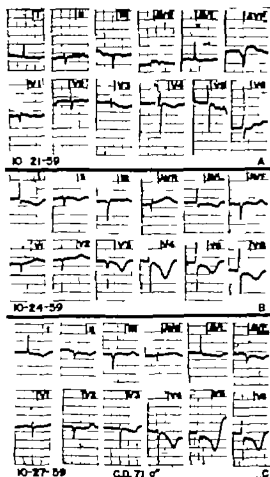


Fig. 5. Case 4. C.D., 71-year-old man with coronary artery disease and acute cerebral embolism. A. Electrocardiogram on Oct. 21, 1959 shows auricular fibrillation, old inferior myocardial infarction, marked ventricular irritability and nonspecific changes in the T wave. B. Tracing obtained 3 days later shows typical T-wave inversion and widening, as well as prolongation of the Q-T time. The electrolyte levels were normal. C. Three days later there was essentially no change in the electrocardiogram; again, normal electrolyte levels were present.

placed on Dicumarol and gradually improved. He never developed any clinical symptoms or signs which suggested coronary insufficiency or myocardial infarction. He died suddenly 2 months later. No autopsy was permitted.

Case 5. J.G., BCH #1695128, an 85-year-old man was hospitalized in an unconscious state with paralysis of both lower extremities. There was no evidence of heart disease. The electrocardiogram on admission showed prolongation of the Q-T

Table I. Case 2. Laboratory data in Patient J.H.

Date	*Hematocrit*	*Blood urea nitrogen (mg. %)*	*Sodium (mEq.)*	*Potassium (mEq.)*	*Chloride (mEq.)*	*Carbon dioxide (mEq.)*
Nov. 23, 1959	48	16	—	—	—	—
Dec. 11, 1959	44	21	138	5.0	94	30
Jan. 1, 1960	—	144	162	9.0	135	11.8

Table II. Case 3. Laboratory data in Patient M.L.

Date	*Hematocrit*	*Blood urea nitrogen (mg. %)*	*Sodium (mEq.)*	*Potassium (mEq.)*	*Chloride (mEq.)*	*Carbon dioxide (mEq.)*	*Calcium (mg. %*)*
March 1960	45	26	—	—	104	28.5	—
March 9, 1960	—	26	144	4.3	100	23.5	10.5
April 1960	40	17	133	4.2	91	26	—

*Range of normal 22 to 43 units.

Table III. Case 4. Laboratory data in Patient C.D.

Date	*Hematocrit*	*Nonprotein nitrogen (mg. %)*	*Sodium (mEq.)*	*Potassium (mEq.)*	*Chloride (mEq.)*	*Carbon dioxide (mEq.)*
Oct. 22, 1959	14.8	[illegible]	147	4.5	101	25
Oct. 24, 1959	15.6	—	138	3.7	100	[illegible]
Oct. 27, 1959	16.0	—	138	4.2	97	27
Oct. 30, 1959	—	—	—	—	—	—
Nov. 2, 1959	—	—	142	4.4	104	26

interval and deeply inverted T waves (Fig. 6,A). Electrolytes at this time showed evidence of some dehydration (Table IV). A neurological consultant diagnosed diffuse as well as focal brain disease—most likely the consequence of multiple cerebral infarcts. The electrocardiogram which was taken after restoration of the fluid balance still showed slight prolongation of the Q-T interval, and the T waves were more deeply inverted (Fig. 6,B).

Case 6. J.R., BCH #1701522, was a 64-year-old

Calcium (mg %)	*Phosphorus* (mg %)	*Rhythm and additional ECG diagnoses* (Oct. 28, 1959)	*Rate*	*Q-T interval* (sec.)	*Precordial*	
					T wave	*U wave*
10.7	4.8	Auricular fibrillation digitalis effect	80	0.38	Positive	–
10.0	—	Auricular fibrillation (Dec. 30, 1959)	62	0.58	Negative	+
—	—	Auricular fibrillation	100	0.33	Positive and peaked	–

Phosphorus (mg %)	*SGOT** units	*Rhythm and additional ECG diagnoses*	*Rate*	*Q-T interval* (sec.)	*Precordial*	
					T wave	*U wave*
—	62	Auricular fibrillation, right ventricular hypertrophy	100	0.46	Positive	+
2.6	44	Auricular fibrillation, right ventricular hypertrophy	84	0.52	Negative	+
—	—	Auricular fibrillation, right ventricular hypertrophy	78	0.36	Negative	+

SGOT units	*Rhythm and additional ECG diagnoses*	*Rate*	*Q-T interval* (sec.)	*Precordial*	
				T wave	*U wave*
—	Auricular fibrillation, multiple ventricular premature beats, digitalis excess?	70	0.44	Negative	+
—	Old inferior infarction	65	0.50	Negative	+
—	As above	55	0.50	Negative	±
35	—	50	0.48	Negative	+
—	—	—	—	—	–

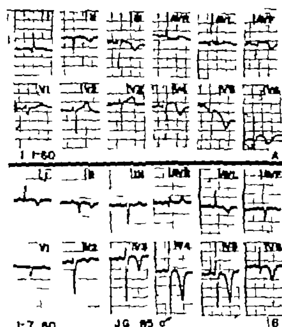


Fig. 6. Case 5. J. G., 85-year-old man with diffuse and focal brain disease. *A*, On Jan. 1, 1960, S-T-segment and T-wave abnormalities were noted while extensive neurological changes were present. *B*, Six days later, persistence of electrocardiographic abnormalities in the presence of normal levels of serum electrolytes.

n who entered the Neurosurgical Service with signs and symptoms indicative of a subdural hematoma. Abnormal S-T-segment elevation, prolongation of the Q-T interval, and wide T wave inversion were observed shortly after admission while an arteriogram was being taken. During the procedure the blood pressure dropped to 80/60 mm. Hg. The day after this episode the subdural hematoma was evacuated. Gradual improvement in the neurological status ensued. The electrocardiogram showed reduction of the Q-T interval to normal, the S-T segments returned to the base line, but no evidence of myocardial damage was shown in the QRS complex. Slight inversion of the T wave in Leads V_1 to V_4 persisted at the time of discharge.

Although myocardial damage may well have occurred after the hypotensive episode which followed cerebral arteriography,[13] the sequence of events suggests a cerebral origin for the electrocardiographic abnormality. Such changes after traumatic cerebral contusions have been described previously.[14]

Discussion

Although the autopsy findings in the first case clearly implicate a cerebral origin of the electrocardiographic alterations, the lack of postmortem data in the other cases leaves the possibility of primary cardiac disease as a causative agent. Also some of the neurological manifestations may have been secondary to cardiac disorders. However, the clinical observations and the sequence of events strongly suggest that in these patients the profound electrocardiographic changes may have been produced by extracardiac influences in the absence of heart disease and electrolyte disorders.

The first suggestion that electrocardiographic abnormalities may be observed in patients with cerebral disease was made by Byer, Ashman, and Toth.[15] Similar observations were made in a detailed report by Burch and associates[1] in 1954. In 17 cases they described a prolonged Q-T interval and large, occasionally negative, T waves in the standard and chest leads. It was stated that some of the widest and largest T waves seen in clinical electrocardiography were recorded in this syndrome, and furthermore that the most pronounced changes seemed to occur in subjects with cerebral hemorrhage. In a communication appearing in 1956 Wasserman and co-workers[3] were able to demonstrate in 12 patients with various cerebral vascular accidents that such marked prolongation of the Q-T interval

Table IV. Case 5. Laboratory data in Patient J. G.

Date	Hematocrit	Blood urea nitrogen (mg. %)	Sodium (mEq.)	Potassium (mEq.)	Chloride (mEq.)	Carbon dioxide (mEq.)
Jan. 1, 1960	45	59	160	4.7	109	30
Jan. 8, 1960	—	—	147	5.3	105	23
Jan. 15, 1960	—	30	—	4.8	107	—

and prominent alterations of the T wave occurred without coexistent electrolyte disturbances. They thought that changes in the hypothalamus were the chief factor responsible inasmuch as electrolyte changes and in those examined at autopsy myocardial infarction could not be held responsible.

Of a group of 29 patients with intracranial hemorrhage recently observed by Cropp and Manning[4] 15 showed abnormal electrocardiograms. Fourteen had prolonged Q-T intervals and a large number had T wave changes similar to those described above. Angiograms localized the lesion to the anterior fossa in 11 patients. This includes the area in which the lesions were found in Patient E. M (Case 1) They demonstrated typical electrocardiographic changes in at least one patient after manipulation of the carotid artery and stimulation of area 13 of the cerebral cortex. This area has cortical representation of the vagus nerve.

A recent communication from China[16] on 44 patients with cerebral vascular accidents, including 7 with subarachnoid hemorrhage, describes prominent U waves in 33 prolonged Q-T intervals in 32 and large inverted T waves of the type mentioned earlier in 2 patients. In all of these the electrolyte levels were determined at the time of the electrocardiographic changes and were found to be normal In none was associated myocardial infarct thought to be present.

There are isolated reports of massive T-wave inversions. In the electrocardiograms of 2 of the 3 patients discussed by Ippolito and associates[17] the T waves have an appearance identical to those in our tracings It is of interest to note that although a slow ventricular rate was held to be responsible for these changes both patients were found to suffer from repeated syncopal attacks. Unfortunately no electrolyte studies were reported.

In some experimental investigations into this subject, embolism was produced by means of injection of paraffin-oil into the carotid artery.[2,18] Náva and co-workers[2] controlled their experiments with simultaneous determinations of the coronary flow pulmonary arterial pressure and peripheral blood pressure. Shortly after injection of the paraffin classic changes, which consisted of prolonged Q-T time deeply inverted T waves and bradycardia were seen in most animals. This was not observed in animals in which a vagotomy had been performed previously Roganti and associates[18] increased the pressure in the central nervous system by adding an inert fluid to the cerebrospinal fluid and also noted T-wave inversion with prolongation of S-T time in their experimental animals. Unfortunately the relationship between time of stimulation and onset of electrocardiographic alterations was not given.

Barger and associates[19] were able to show that, after infusion of epinephrine and norepinephrine into a coronary artery of an intact dog deeply inverted T waves and depressed S-T segments would result persistently without a rise in serum lactic dehydrogenase. These findings suggest that an adrenergic reflex can produce a persistent alteration of the electrocardiogram of the type described above without preceding myocardial necrosis.

In this respect a recent report by Wein

Phosphorus (mg. %)	*Rhythm and additional ECG diagnoses*	*Rate*	*Q-T interval (sec.)*	*Precordial*	
				T wave	*U wave*
—	Normal sinus rhythm	73	0 39	Negative	+
—	Normal sinus rhythm	79	0 41	Negative	–
3 7	—	—	—	—	—

berg and Fuster[18] is of interest they discuss their results of stimulation of numerous points of the midbrain of the cat. After necropsy a correlation was attempted between the localization of the anatomic sites stimulated and the various types of changes observed on the electrocardiogram Hypothalamic irritation resulted in distortions of the T wave and various arrhythmias

It has been well documented by Surawicz and others[20] that changing concentrations of potassium and calcium in the extracellular fluid of the isolated heart of the animal will be reflected in the electrocardiogram by changes in the Q T time and T wave appearance Similar observations have been made in man[11,21] Presumably such changes are the result of altered gradients across the cardiac cell membrane. Since no significant extracellular disturbances could be demonstrated in our cases, it appears attractive to postulate that there may be intracellular alterations of electrolyte concentration sufficient to alter the transmembrane potential Furthermore the changes found in our patients differ from those usually found with hypocalcemia or hypokalemia.

Recently Ballard and Sayers[21] presented evidence which indicates that aldosterone has a direct digitalis-like action on the myocardial cell A recent report by Farrell[22] discusses the mechanisms by which the secretion of aldosterone may be regulated from the midbrain Although the exact sites have not been ascertained there appears to be a distinct control by higher nervous centers of the secretion of this steroid

From these data a number of conclusions can be drawn (1) A variety of cerebral disorders (including vascular and neoplastic changes) can cause disturbances in the depolarization and repolarization of the myocardium It is probable that such cerebral abnormalities must involve among other areas the hypothalamic region, either intrinsically or extrinsically (2) It is not established whether such changes may be transmitted through neurogenic (vagus nerve) or humoral pathways or both (3) The electrocardiographic changes in their classic appearance suggest profound electrolyte changes.[11,21] It is likely however that the electrocardiographic changes found in our patients form only a small aspect of the detailed over-all control of cardiac function by higher nervous centers as recently reviewed by Rushmer and Orville[24]

In the current report, attention has been called to the existence of electrocardiographic alterations in cerebral disorders. Possible etiological factors have been discussed Further investigations are now being carried out in our laboratory in regard to the exact mechanism of production of these abnormalities.

Conclusion and summary

Striking prolongation of the Q-T interval deeply inverted widened T waves and prominent U waves were observed in 6 patients with cerebral disorders. Although these changes were indistinguishable from electrolyte disorders in the extracellular fluid electrolyte determinations were all within normal limits. The close association of these alterations with cerebral disease suggests cerebral influence on if not control of cardiac repolarization

We are indebted to Dr H D Levine for his kind permission to report Case 1 and to Dr L. B. Ellis and Dr D E Denny-Brown for their review of the manuscript

REFERENCES

1 Levine, H. D Non-specificity of the electrocardiogram associated with coronary artery disease, Am. J Med. 15:344 1953
2 Burch, G E., Meyers, R., and Abildskov J A. A new electrocardiographic pattern observed in cerebrovascular accidents, Circulation 9 719 1954.
3 Wasserman, F Choquette, G Cassinelli, R., and Bellet, S.: Electrocardiographic observations in patients with cerebrovascular accidents, Am. J M Sc. 231:502, 1956.
4 Cropp, G J and Manning G W Electrocardiographic changes simulating myocardial ischemia and infarction associated with spontaneous intracranial hemorrhage Circulation 22:25 1960.
5 Shuster S.: The electrocardiogram in subarachnoid hemorrhage Brit Heart J 22:316, 1960.
6 DiPaolo, E., and Orlandi, G: La sindrome cerebro-cardiaca acuta Arch. Maragliano pat. e clin. 14 143 1958.
7 Korenevskaia, T Electrocardiography in organic central nervous system lesions, Terap. Arkh 30:43, 1958
8 Mucio, G et al.: Modificazioni elettrocardiografiche in corso di incidente vascolari cerebrali, Minerva med 43 733, 1952.

(cont) ...

9. Náva, S., et al.: Hemodynamic and electrocardiographic aspects of experimental cerebral embolism, Minerva med. 48:3289, 1957
10. Weinberg, S. J. and Fuster J. M. Electrocardiographic changes produced by localized hypothalamic stimulations, Ann. Int. Med. 53:332, 1960.
11. Kowalski, H. J. and Abelmann, W. H.: The cardiac output in Laennec's cirrhosis, J. Clin. Invest. 32:1025, 1953.
12. Spodick, J. H.: Hypocalcemic electrocardiographic abnormalities in diseases of the liver Am. Heart J 57:118, 1959
13. Greitz, T. and Weiss, S. C. EEG and ECG in cerebral angiography with sodium diatrizoate (Hypaque) and methylglucamine diprotrizoate (Miokon) Acta radiol. 42:145, 1959
14. Kenedi, I. Electrocardiographic changes of neural origin, Magyar Belorv Arch. 12:30, 1959
15. Byer E., Ashman, R., and Toth, L. A. Electrocardiograms with large upright T waves and long Q-T intervals, Am. Heart J 33 796, 1947
16. Kung L. S., et al. The electrocardiogram in cerebrovascular accidents, Chinese M. J. 76:445 1958.
17. Ippolito, T. L., Blier J. S., and Fox, T. T.: Massive T-wave inversion, Am. Heart J 48:88, 1954
18. Roganti, M. et al. Electrocardiographic changes in the course of cerebrovascular accidents, Arch pat. e clin. med. 35:10 1958.
19. Barger A. C., Liebowitz, M. R., and Herd, J. A.: Chronic catheterization of the coronary artery: infusion of autonomic drugs in the unanesthetized dog Fed. Proc. 20 107 1961
20. Surawicz, B. Lepeschkin E., Herrlich, H. C., and Hoffman, B. F. Effect of potassium and calcium deficiency on the monophasic action potential, electrocardiogram and contractility of isolated rabbit hearts, Am. J. Physiol. 196:1302, 1959
21. Bellet, S., and Finkelstein, D. Significance of Q-T prolongation in the electrocardiogram, Am. J. M. Sc. 222:263, 1951
22. Ballard, K. W., and Sayers, G. Stimulatory effect of aldosterone and cortisol on the work of the isolated rat heart-lung. Abstract presented to the Forty-first Annual Meeting of the Endocrine Society 1957
23. Farrell, G. A. Adrenoglomerulotropin, Circulation 21 1009 1960.
24. Rushmer R. F. and Orville, A. S. Jr. Cardiac control, Physiol Rev 39:41 1959

Ineffectiveness of anticoagulants in myocardial infarction

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The use of anticoagulants in the management of acute myocardial infarction is a widespread practice accepted by most clinicians as of considerable value. Published data on which this acceptance is based are numerous but only rarely include well-documented controls. Schnur[1] pointed out in 1953 that the prognosis of myocardial infarction is a function of many factors other than the simple presence of infarction and that in order to serve as controls a group of patients with this diagnosis must be comparable in all ways to those in the treated group. He devised a system for evaluating the degree of illness of patients, the Pathologic Index Rating (PIR) by assigning numbers to various findings such as cardiac decompensation, arrhythmia, shock, etc (Table I). Use of this system allows patients with similar severity of illness to be paired for evaluation of treatment. His experience indicated that prognosis was predictable from the PIR and that the use of anticoagulants did not alter the predicted mortality. Smart and Bruce[2] applied the same criteria in a study of their patients with myocardial infarction and confirmed the finding that higher Pathologic Index Ratings are associated with higher mortality rates. Their[2] evaluation of the effectiveness of anticoagulants in the management of myocardial infarction showed no significant difference between the mortality rates of the control group and those of the treated groups when patients in the same PIR category were compared. The purpose of this paper is to report on another series in

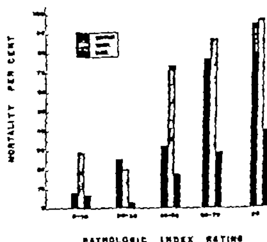


Fig 1 Comparison of mortality rates in acute myocardial infarction in three series. See text.

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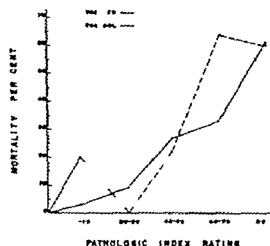


Fig. 2. Hospital mortality in acute myocardial infarction (exclusive of deaths which occurred within 24 hours). Combined data from present study and that reported by Schnur. See Table II.

which experience with anticoagulants in the treatment of acute myocardial infarction is compared to that without these drugs in patients with the same degree of illness.

Material and methods

The records of 148 patients with acute myocardial infarction who were treated in the University Hospital between July 1, 1955 and June 30, 1960 were reviewed. In each case the diagnosis was established by electrocardiography, SGOT values, other supportive laboratory studies, the clinical picture, and in some cases, autopsy findings. Twenty of these patients died within 24 hours of the onset of symptoms and were omitted from the study because anticoagulant therapy could not have been expected to influence their course and because we desired to use the same criteria that Schnur and Smart had used for selection of patients. In each of the other 128 patients the PIR was determined using Schnur's criteria, from findings on the day of admission. In addition, data for prothrombin activity in each patient were tabulated.

Results

Fig. 1 shows the results of the present study compared with those of the other

*Table I. Information obtained from clinical records, ratings for various clinical findings, and method of determining Pathologic Index Rating**

Information obtained from clinical records	
Date of admission	Congestive heart failure
Age	Serious arrhythmia
Sex	Associated serious diseases: pulmonary, renal, other
Results: lived or died	History of serious vascular or other disease
Died: within 24 hr. or later	
Shock	

Pathologic Index Ratings					
Shock		40	Associated serious diseases		10-25
			Diabetes	10-25	
Congestive failure		20-25	Uremia	10-25	
			Urinary tract infection	10	
Serious arrhythmias		10-40	Emphysema	10	
Occasional ventricular contractions	10		Cerebral thrombosis	10-25	
Frequent ventricular contractions	15				
Auricular tachycardia	15		History of heart or vascular disease		10-30
Auricular fibrillation	25		Hypertension	10	
Auricular flutter	30		Cardiac enlargement	15	
Ventricular tachycardia	40		Angina	10-30	
			Congestive failure	20-30	
Gallop rhythm		15	Previous coronary occlusion	20-30	

*Criteria for assessment of severity of illness of patients with acute myocardial infarction (from Schnur: Circulation 7:855, 1953, by permission).

Table II Hospital mortality in acute myocardial infarction (exclusive of deaths which occurred

PIR	0-19				20-39			
	Treated		Control		Treated		Control	
	Patients	M.R. (%)	Patients	M.R. (%)	Patients	M.R. (%)	Patients	M.R. (%)
Mississippi	33	3	8	25	25	4	4	0
Texas	38	3	2	0	22	14	4	0
Combined	1	3	10	20	47	9	8	0

Treated: Received anticoagulant. M.R.: Mortality rate.

published studies in which the same methods were used. Mortality rates are for all patients in the series and it is clear that increasing PIR is associated with increasing mortality rate.

The hospital mortality rate for all 128 patients considered as a single group was 5 per cent; for the treated group of 100 it was 11 per cent, and for the control group of 28 patients who received no anticoagulants it was 29 per cent. These figures seem at first to support the view that benefit was derived from anticoagulant therapy but further analysis shows that such was not the case. The average PIR for the treated group was 37, whereas for the control group it was 43; this is to say that the treated group had a better prognosis in the beginning. Table II shows the mortality rates from the present series together with those reported by Schnur. Fig. 2 presents the same data in graphic form and demonstrates that the increase in mortality rate associated with increase in PIR is not affected significantly by treatment. Tested by the chi-square method, the differences between the control group and the treated patients in each group are found to be insignificant; they could have occurred easily by chance alone.

Nine of the treated patients were given only heparin but consistently prolonged clotting time was not demonstrated in any of these. Ninety-one were treated with prothrombopenic drugs, usually Dicumarol. Excluding the first 3 days of therapy, when the effect of the drug could not be expected to be fully developed, there were 1,295 prothrombin determinations in these patients, an average of a determination on 3 out of 4 days for each patient. Of these only 28 per cent were within the therapeutic range (5 to 10 per cent prothrombin activity by the Quick one-stage method using deprothrombinized plasma). If determinations which represent overtreatment (those with prothrombin activity less than 5 per cent of normal) are included as evidence of adequate therapy, the figure rises to 55 per cent.

Discussion

Two points have been emphasized by the results reported. First, if a method of therapy is to be assessed by clinical trial it must be the only variable; that is, patients in the control group must be selected very carefully to match those in the treated group in every pertinent respect. A young man otherwise healthy hospitalized for his first myocardial infarct without complications has a prognosis different from that of a patient whose present infarct is comparable but who has had one before, has suffered from angina for years, is in congestive heart failure, and has diabetes. Nevertheless, it has been the practice to attempt to evaluate the effectiveness of anticoagulant therapy in myocardial infarction without considering such variables. The few studies in which patients with comparable degrees of illness have been paired have not shown that the patients received any benefit from the use of anticoagulants.[1,3,4]

The second point concerns the considerable difference between achieving adequate anticoagulation and merely giving

within 24 hours)

40-59				60-79				80+			
Treated		*Control*		*Treated*		*Control*		*Treated*		*Control*	
Patients	*M.R.* (%)	*Patients*	*M.R.* (%)	*Patients*	*M.R.* (%)	*Patients*	*M.R.* (%)	*Patients*	*M.R.* (%)	*Patients*	*M.R.* (%)
22	18	7	14	9	11	5	60	11	36	4	50
8	50	2	50	6	67	3	67	7	100	1	100
30	27	9	22	15	33	8	63	18	61	5	60

anticoagulants. Granted that the prothrombin time is an inaccurate determination of uncertain significance it is the means by which the dose of prothrombopenic anticoagulants is determined and provides almost the only evidence available that anticoagulation has been achieved. Few reports in the literature which purport to show benefits from anticoagulation in myocardial infarction actually document prothrombin suppression of a degree thought to be associated with impaired intravascular clotting The only report of the incidence of adequate prothrombin suppression in a large series of patients under treatment for myocardial infarction which we found for comparison with the 28 per cent in this series is 33 per cent reported by Schnur[1]

In most instances, accuracy would be served better by reference to coumarin therapy instead of anticoagulant therapy Effects of these drugs other than those concerned with the clotting mechanism include vasodilatation[6,7] increased excretion of uric acid[8] and even relief of pain decrease in adhesiveness of platelets and increase in the rate of recanalization of thrombi.[9] The significance of these little-studied phenomena is speculative but must be considered

Summary and conclusion

The ineffectiveness of anticoagulant drugs as they are used at present has been documented in a group of patients with acute myocardial infarction. The importance of comparable controls in the assessment of the results of any treatment has been emphasized and the question of anticoagulation versus the use of anticoagulants has been discussed.

Addendum

Since this paper was submitted for publication a prospective and more impressive study the results of which cast further doubt on the usefulness of anticoagulants in myocardial infarction has been published.[10]

REFERENCES

1. Schnur S. Mortality and other studies questioning the evidence for and value of routine anticoagulant therapy in myocardial infarction, Circulation 8:855 1953
2. Smart, T B and Bruce, R. A. Relationship of mortality from myocardial infarction to pathologic findings and age, Am. J M. Sc. 230:380 1955
3. Bruce, R. A Personal communication, 1961.
4. Carleton, R. A., Sanders, C. A., and Burack, W R Heparin administration after acute myocardial infarction, New England J Med. 263 1002 1960
5. Bingham J B Meyer O O and Pohle, F J Studies on the hemorrhagic agent 3,3'-methylene (4-hydroxycoumarin) I Its effect on prothrombin and coagulation times of the blood of dogs and humans, Am. J M Sc. 202:563 1941
6. Bollman, J L., and Preston, F W The effects of experimental administration of dicoumarin, J.A.M.A. 120 1021 1942.
7. Blake, T M Wood, E. G Jr., O'Moore, D., Neel, R. G. Vasodilating effects of coumarin derivatives, Am. J M Sc. (to be published)
8. Hansen, O E., and Holten, C. Uricosuric effect of Dicoumarol, Lancet 1 1047 1955.
9. Garb Solomon The current status of anticoagulants in the treatment of myocardial infarction, Am. J M Sc. 229:534, 1955.
10. Hilden, T., Raaschou, F., Iversen, K. and Schwartz, M.: Anticoagulants in myocardial infarction, Lancet 2:327 1961.

The vectorcardiogram in left ventricular hypertrophy

A study using the Frank lead system

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This report is concerned with the vectorcardiographic findings in left ventricular hypertrophy The data presented will be limited to a detailed analysis of the QRS loop, although we recognize that complementary information of electrogenic importance may also be found in P and T loops. Twenty four adult patients constitute the study group The circulatory stress which led to left ventricular hypertrophy was of the systolic overload type[1] in each instance One hundred normal subjects served as a control group

Qualitative and quantitative descriptions of the frontal horizontal and right sagittal projections of the spatial vectorcardiogram will be presented The discussion stresses the significant points of difference between the loops recorded from normal subjects and those recorded from patients with left ventricular hypertrophy An attempt will be made to integrate our present knowledge of the anatomic and electrophysiologic sequelae of left ventricular hypertrophy with the vectorcardiographic loops recorded at the body surface.

Methods

The Frank[2] lead system was used in this study with 50,000 ohms as the unit of resistance. The chest electrodes were placed at the level of the fifth intercostal space and the recordings were made with the subjects in the supine position The three scalar components X Y and Z were amplified by Sanborn 350-3,200 preamplifiers and recorded on an Ampex FR 100A magnetic tape recorder at a tape speed of 60 inches per second (i p.s.) The tape was later played back at a speed of 1 7/8 i p.s. (time expansion factor 32) into a Tektronix Type 502 dual beam oscilloscope. The loops were interrupted at a rate of 15 6 per second (500 times per second at the original speed) Frontal horizontal and right sagittal projections of the interrupted and *uninterrupted loops were photographed* with a Hewlett Packard oscilloscope camera Scalar tracings of the X Y and Z leads were made on a Consolidated Engineering Oscillograph recorder Standard 12 lead electrocardiograms were recorded with either the Sanborn Twin Beam photographic recorder or the Sanborn Twin-Viso direct writing recorder Details of our recording system are presented elsewhere.[3]

The three projections of the spatial QRS loops were drawn to scale from the photographs, and the Q R and S loops were defined The angle magnitude, and time

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of occurrence of the Q R, and S vectors were measured in each plane as well as the length width and duration of the entire loop. The angle and magnitude of "J" displacement were noted. The magnitudes of the spatial Q R, and S vectors were calculated according to the Pythagorean formula. A detailed description of our technique of analysis of the loops is presented in a previous paper.[4]

The study group consisted of 24 male patients who ranged in age from 35 to 74 years (mean of 51 years) The patients had either hypertensive vascular disease or significant aortic stenosis. Each patient had a diffuse sustained apical impulse as determined by physical examination. The clinical impression of left ventricular hypertrophy was supported in 22 by routine 12 lead electrocardiograms and in 21 by chest x-ray examinations. Patients with a history of myocardial infarction or angina pectoris, or an electrocardiogram that was believed to be diagnostic of previous myocardial infarction were not included in this study Patients with evidence of significant aortic insufficiency or mitral insufficiency were excluded Patients who, on routine electrocardiographic examination revealed evidence of typical bundle branch block were also excluded as were any with a QRS duration which exceeded 120 milliseconds.

The purpose of the above-described method of selection of patients was to insure the presence in each instance, of left ventricular hypertrophy of the systolic overload type and to exclude patients with manifest coronary artery disease left ventricular diastolic overload or conduction delay typical of bundle branch block. The clinical features of the study group are presented in Table I

Results

A Frontal plane (*Table II*) A Q loop could be defined in only 11 of the 24 patients. In the other 13 the efferent limb of the tracing started directly to the left and usually inferiorly In these cases no Q loop was demonstrable The initial forces in the frontal plane are illustrated in Fig. 1 The R vector was directed to the left in each instance and inferiorly in 20 of the 24 patients. The R loop was written in a counterclockwise direction in the majority of cases.

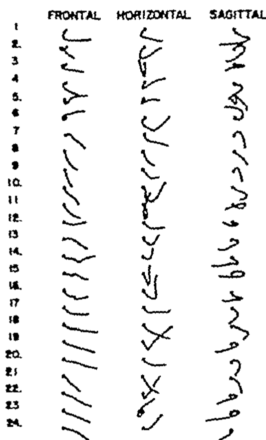


Fig 1 The initial forces of the vectorcardiogram in each plane. The case numbers correspond with those in Table I.

An S loop could be defined in only 4 of the patients. Thirteen patients showed "J" displacement. In this plane 3 patients had clockwise QRS loops, 13 had counterclockwise QRS loops, and 8 had figure-of-eight loops.

B Horizontal plane (*Table III*) In the horizontal plane a Q loop could be defined in 18 of 24 patients. In these 18 the Q vector was directed anteriorly and either to the right or left. The initial forces in the horizontal plane are illustrated in Fig 1 The R vector was directed posteriorly in 23 of the patients. An S loop could be defined in only 2 patients. In the other 22 the afferent limb was straight. "J displacement was evident in 14 patients. One patient had a clockwise loop in the horizontal plane 14 had counterclockwise loops and 9 had figure-of-eight loops.

C. Sagittal plane (*Table IV*) In the sagittal plane a Q loop could be defined

Table I Clinical data. Left ventricular hypertrophy

Case number	*Age (yr.)*	*Blood pressure (mm. Hg)*	*Left ventricular systolic pressure*	*Physical examination*	*X-ray*	*ECG**	*Digitalis*	*Congestive heart failure*
1	57	170/120	—	+	+	+	+	+
2	49	240/140	—	+	+	+	+	+
3	45	150/100	—	+	+	+	+	+
4	39	180/120	—	+	+	+	0	0
5	53	230/140	—	+	+	±	+	0
6	45	190/130	—	+	+	+	0	0
7	50	170/100	—	+	±	±	0	0
8	35	220/145	—	+	+	+	0	0
9	72	150/100	—	+	±	+	0	0
10	43	215/130	—	+	+	+	+	+
11	44	150/115	—	+	+	+	+	+
12	65	170/120	—	+	+	+	+	+
13	67	180/100	—	+	+	+	0	0
14†	74	100/80	—	+	+	+	+	+
15†	54	100/60	183	+	+	+	+	+
16	64	160/90	—	+	+	+	+	+
17†	49	117/80	240	+	+	+	+	0
18	72	180/90	—	+	+	+	0	0
19†	35	89/42	220	+	+	+	0	0
20	40	200/110	—	+	±	+	0	0
21	49	260/160	—	+	+	+	+	0
22	39	185/150	—	+	+	+	+	+
23	37	210/140	—	+	+	+	0	0
24	51	265/140	—	+	+	+	0	0

*Refers to the presence or absence of hypertrophy by this technique.
†Aortic stenosis.

in 22 of the 24 patients. The Q vector was directed anteriorly and usually inferiorly. The initial forces in the sagittal plane are illustrated in Fig. 1. The R vector was directed posteriorly in all cases. S loops could be defined in only 5 patients. "J" displacement was evident in 11. Nineteen of the patients had clockwise loops in this plane and 5 had figure-of-eight loops.

D. Spatial data (Table V). The magnitudes of the spatial Q and R vectors were calculated. Values for the S vector are not presented because of their infrequent occurrence.

Special considerations. In the horizontal plane three distinct types of loops were seen. The first type was inscribed entirely in a counterclockwise direction. The second type was oriented more posteriorly and had a small clockwise tip to the R loop. The third type was also oriented posteriorly and had a major clockwise inscription of the R loop. Examples of each type are presented in Figs. 2, 3, and 4. A comparison of Type I and Type III loops revealed several significant differences. This comparison is presented in Table VI. The results indicate that Type III loops differ from Type I loops by (a) being oriented more posteriorly, (b) having an increase in QRS magnitude, (c) having a leftward rather than rightward Q loop, (d) having a major clockwise inscription of the R loop, (e) having a longer QRS duration as well as delay in inscription of the R point, and (f) having intermediate and/or terminal slowing.

Type II loops were intermediate between Type I and III loops with respect to each of the above-noted measurements.

COMPARISON BETWEEN LOOPS RECORDED FROM NORMAL INDIVIDUALS AND THOSE FROM PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY (TABLES I TO VI)

A. *Frontal plane.* In the frontal plane most normal subjects had an initial Q loop which was written to the right and superiorly. In left ventricular hypertrophy the

*Table II Frontal plane data**

	Q angle (degrees)	Q magnitude (mv)	Q time (msec)	R angle (degrees)	R magnitude (mv)	R time (msec)	Loop length (mv)	Loop width (mv)	L/W ratio	QRS duration (msec)
Normal										
Mean	−150	0.10	8	+36	1.25	35	1.39	0.29	5.97	76
S.D	±56	±0.06	±3	±13	±0.33	±6	±0.35	±0.15	±3.63	±10
LVH										
Mean	+134	0.11	7	+14	2.15	45	2.27	0.58	5.12	86
S.D	±43	±0.02	±3	±35	±0.77	±8	±0.78	±0.36	±3.17	±22
Difference means	76	0.01	1	22	0.90	10	0.88	0.29	0.85	10
p Value	<0.001	>0.50	<0.40	<0.001	<0.001	<0.001	<0.001	<0.001	<0.40	<0.001

*Presented are the mean and one standard deviation for the normal group as well as for patients with left ventricular hypertrophy (LVH). The p value for the difference is also noted.

Table III Horizontal plane data

	Q angle (degrees)	Q magnitude (mv)	Q time (msec)	R angle (degrees)	R magnitude (mv)	R time (msec)	Loop length (mv)	Loop width (mv)	L/W ratio	QRS duration (msec)
Normal										
Mean	+114	0.16	10	+1	1.03	37	1.18	0.67	2.05	82
S.D	±25	±0.09	±4	±18	±0.32	±3	±0.35	±0.29	±1.10	±8
LVH										
Mean	+87	0.26	9	−28	2.43	48	2.62	1.01	3.11	94
S.D	±35	±0.13	±4	±20	±0.82	±6	±0.86	±0.44	±1.54	±12
Difference means	27	0.10	1	29	1.40	11	1.44	0.34	1.06	12
p Value	<0.001	<0.001	<0.20	<0.001	<0.001	<0.001	<0.001	<0.001	<0.01	<0.001

Table IV Right sagittal plane data

	Q angle (degrees)	Q magnitude (mv)	Q time (msec)	R angle (degrees)	R magnitude (mv)	R time (msec)	Loop length (mv)	Loop width (mv)	L/W ratio	QRS duration (msec.)
Normal										
Mean	−19	0.15	11	+96	0.81	37	0.96	0.61	1.79	83
S D	−33	±0.08	±4	±23	±0.33	±4	±0.35	±0.26	±0.94	±17
LVH										
Mean	+23	0.22	8	+145	1.54	44	1.79	0.89	2.84	92
S D	±29	±0.11	±4	±36	±0.61	±7	±0.40	±0.51	±1.99	±11
Difference means	42	0.07	3	49	0.73	7	0.83	0.28	1.05	9
p Value	<0.001	<0.005	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.005

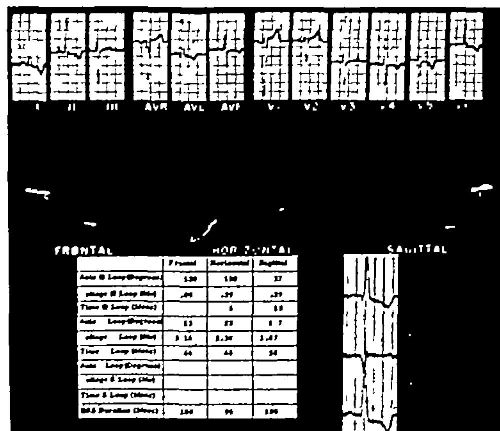


Fig. 2. Case 4. Type I loop. Note the rightward initial force and the open counterclockwise QRS_H loop.

Q loop was frequently absent. When present the Q loop was oriented inferiorly. The magnitude of the Q vector in the frontal plane did not differ from that of normal subjects. The time of inscription of the Q vector was also normal. The R vector was displaced to the left in those with ventricular hypertrophy. There was also a significant increase in the magnitude of the R vector and a delay in its time of occurrence. Normal subjects had a terminal S loop which was usually oriented to the right and either superiorly or inferiorly. In left ventricular hypertrophy the entire afferent limb of the QRS complex was displaced superiorly and returned to the origin as a smooth curve with no terminal S deflection.

Table V. Magnitude of the spatial Q and R vectors

	Spatial magnitude (mv.)	
	Q vector	R vector
Normal		
Mean	0.17	1.32
S.D.	±0.09	±0.41
Hypertrophy		
Mean	0.29	2.55
S.D.	±0.19	±0.80
Difference means	0.12	1.23
p Value	<0.001	<0.001

B. Horizontal plane. In the horizontal plane normal subjects had a Q vector which was directed anteriorly and usually to the right. Patients with left ventricular hypertrophy and Type I loops had normally directed Q vectors. In those with Type III loops the Q vector was directed to the left. The magnitude of the Q vector was significantly greater than normal in all types. In the patients with left ventricular hypertrophy the R vector was displaced

posteriorly in nearly all cases its magnitude was greater than normal and there was significant delay in its time of occurrence. The afferent limb of the QRS tracing was straight, with no terminal S loop in the majority of cases. Both the length and width of the loops were significantly greater than normal.

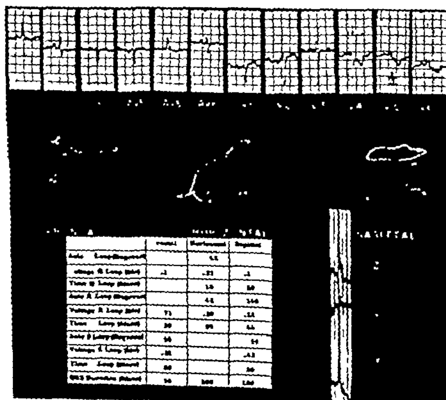
C. Sagittal plane In the sagittal plane all patients with left ventricular hypertrophy had initial anterior forces, and in 22 a distinct Q loop could be defined The Q vector is usually oriented superiorly in normal subjects. The Q vector was directed inferiorly in nearly all the patients with left ventricular hypertrophy The magnitude of the Q vector was significantly greater than normal. The direction of the R vector was more posterior than normal and there was significant delay in the time of its occurrence. The afferent limb of the QRS loop was straight, with no terminal S deflection in the majority of the patients.

In patients with left ventricular hypertrophy the duration of the QRS complex was significantly prolonged in all planes.

D Spatial data The magnitudes of the spatial Q and R vectors were significantly greater than normal in patients with left ventricular hypertrophy A linear correlation was established between the magnitude of the spatial Q vector and that of the spatial R vector

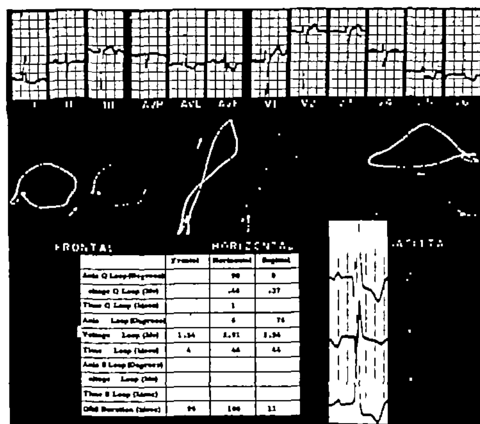
Discussion

The vectorcardiographic findings in 24 patients with left ventricular hypertrophy have been presented. The data are limited to a quantitative analysis of the QRS loop. Each subject reported on in this study was selected on the basis of having (a) a clinical disorder (hypertensive vascular disease or aortic stenosis) which is known to lead to left ventricular systolic overload and (b) strong clinical evidence of left ventricular hypertrophy Patients with manifest coronary artery disease, left ventricular diastolic overload or typical bundle



	Frontal	Horizontal	Sagittal
Axis Loop (Degrees)		55	
Voltage R Loop (MV)	.3	.33	.3
Time R Loop (Msec)		16	50
Axis R Loop (Degrees)		41	140
Voltage R Loop (MV)	75	.50	.34
Time Loop (Msec)	30	95	44
Axis S Loop (Degrees)	50		14
Voltage S Loop (MV)	.18		.43
Time Loop (Msec)	60		30
QRS Duration (Msec)	56	[illegible]	[illegible]

Fig 5 Case 11 Type II loop. Note the leftward initial force, the small clockwise R tip in the horizontal plane, and the terminal slowing



	Frontal	Horizontal	Sagittal
Axis Q Loop (Degrees)		90	0
Voltage Q Loop (Mv)		.44	.37
Time Q Loop (Msec)		1	
Axis Loop (Degrees)		4	76
Voltage Loop (Mv)	1.34	1.81	1.34
Time Loop (Msec)	4	44	44
Axis S Loop (Degrees)			
Voltage Loop (Mv)			
Time S Loop (Msec)			
QRS Duration (Msec)	94	100	11

Fig. 4. Case 11. Type III loop. Note the leftward initial force, the major clockwise rotation of the R loop in the horizontal plane, and the terminal slowing.

inch block were excluded. A statistical comparison of loops recorded from this group of patients and loops from a normal control group revealed significant differences with respect to almost all of the quantitative measurements made. On the basis of this comparison, we have concluded that left ventricular systolic overload of the degree present in these patients was associated with vectorcardiographic changes of the initial, intermediate, and terminal portions of the loop. The method of selection of patients in this study precluded any conclusions about the earliest vectorcardiographic findings in left ventricular hypertrophy and the specificity of the vectorcardiogram in the diagnosis of left ventricular hypertrophy.

The forces recorded during the first 5 to 10 milliseconds were directed anteriorly and inferiorly in the majority of cases. Distinct Q loops were frequently absent in the frontal plane, but could usually be defined in the horizontal and sagittal planes. It is generally agreed that the initial forces of the vectorcardiogram which constitute the Q loop result from left-to-right septal activation. The normal Q vector is directed to the right, anteriorly, and usually superiorly, and is, therefore, consistent with this hypothesis.[4] The Q vector was directed to the right, anteriorly, and inferiorly in those patients who had left ventricular hypertrophy with Type I loops who were thought not to have an intraventricular conduction disturbance. It was believed originally that this might be the result of anatomic rotation of the interventricular septum. However, Grant[6] has shown that this does not occur. Bowing of the interventricular septum with an increase in rightward convexity is seen in the presence of concentric left ventricular hypertrophy and could explain the inferior direction of the Q vector.

In patients with Type III loops the Q vector was directed to the left, anteriorly, and inferiorly. These cases demonstrated

in addition several features which suggest a left intraventricular conduction disturbance. It is our opinion that leftward orientation of the initial forces as seen in this group of patients, is the result of incomplete left bundle branch block. Additional evidence in support of this hypothesis will be presented later in the discussion.

Cabrera and associates[6] have pointed out that one would anticipate the Q vector to be enlarged in proportion to and directed oppositely from the R vector in left ventricular hypertrophy. These changes would presumably result from hypertrophy of the interventricular septum, a fact which has been well documented.[7] However, Cabrera found that the Q loop was frequently reduced in magnitude in a group of patients with left ventricular systolic overload due to a variety of conditions. He postulated that the reduction in magnitude of the Q loop resulted from coronary insufficiency. In our group of patients with left ventricular hypertrophy the magnitude of the spatial Q vector was significantly greater than normal. The magnitude of the spatial Q vector was proportional to the magnitude of the spatial R vector in the majority of cases. Therefore, our data agree with the prediction of Cabrera but not with his findings.

Bryant[8] has pointed out that the initial R waves of right precordial leads are usually not increased in proportion to the increase in QRS magnitude in patients with left ventricular hypertrophy. Frequently they are smaller than normal or even absent. He postulated that this was the result of incomplete left bundle branch block. It is clear from our data that there was no relationship between the spatial magnitude of the initial forces and the height of the initial R wave in right precordial leads. Normally the Q vector is directed superiorly and anteriorly toward precordial electrodes V_1 and V_2. The Q vector was directed inferiorly in left ventricular hypertrophy—therefore partially away from precordial electrodes V_1 and V_2. It was this change in the spatial orientation of the Q vector which accounted for the reduction in height of the R wave in the right precordial electrodes, rather than any reduction in magnitude of the initial forces (see Fig. 5). It also appeared that the reason for the loss of a Q loop in the frontal plane, noted by Cabrera and by us, was this spatial reorientation which precluded visualization in the frontal plane.

It is generally agreed that concentric hypertrophy of one ventricle leads to an increase in the voltage of the vectors which represent depolarization of the involved free wall. The exact mechanism of this increase is not known. Microscopic studies have shown that the individual myocardial fibers are enlarged in cardiac hypertrophy.[9] Experimental studies in hypertensive rats,[10] however, have failed to demonstrate any increase in the transmembrane potential of individual cells in the presence of cardiac hypertrophy. Recent studies by Linzbach[11] have revealed that myocardial hyperplasia occurs in hearts which weigh over 500 grams. The significance of such hyperplasia in determining QRS magnitude is still open to question. Delayed activation of the left ventricular free wall has been suggested by some[12] as a possible cause of the increase in R magnitude. Favoring this hypothesis is the fact that one can acutely alter QRS amplitude in the presence of left

Table VI. A comparison of Type I and Type III loops

Type of loop	Horizontal plane				Spatial magnitude	
	Q angle (degrees)	R angle (degrees)	R time (msec.)	QRS duration (msec.)	Q vector (mv.)	R vector (mv.)
Type I	+105	−15	44	91	0.24	2.12
Type III	+72	−48	55	103	0.33	2.90
Difference means	33	33	9	12	0.09	0.78
p Value	<0.05	<0.001	<0.02	<0.02	>0.20	<0.05

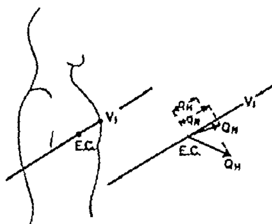


Fig. 5. Note the superior relationship of Lead V_1 to the electrical center (*E.C.*) of the heart. The normal Q vector (*Qn*) is presented with its projection on Lead V_1 (*qn*). Note that the Q vector (*QH*) of left ventricular hypertrophy produces a small projection (*qH*) on Lead V_1 even though it is of greater magnitude.

ventricular hypertrophy by several pharmacologic maneuvers which may primarily influence intraventricular conduction.[13] Against this hypothesis is the fact that an increase in magnitude may occur in the absence of any evidence of conduction delay. In our group of patients the magnitude of the spatial R vector was significantly greater than normal in the presence or absence of evidence for intraventricular conduction delay. A linear correlation was demonstrated between the magnitude of the spatial R vector and the degree of R delay. These findings suggest that the increase in R magnitude seen in patients with left ventricular hypertrophy is not dependent on left ventricular conduction delay but may be exaggerated in the presence of such delay.

Superior displacement of the afferent limb of the QRS loop was seen in 17 of our patients. We were unable to define S loops in 22 of the 24 patients. Mazzoleni and co-workers[15] reporting on the vectorcardiographic findings in 100 patients with left ventricular hypertrophy commented on the frequent superior displacement of the terminal forces (93 out of 100 cases). Cabrera and Gaxiola[4] noted the frequent absence of an S loop in left ventricular hypertrophy as well as superior displacement of the afferent limb; they did not discuss the mechanism involved. Experimental studies on dogs have revealed that the posterobasal region of the interventricular septum and the basal portion of the left ventricular free wall are the last areas to be depolarized.[16] Grant[7] has shown that the basal portion of the left ventricular free wall is hypertrophied, elongated, and bowed superiorly in the presence of left ventricular enlargement. He has further suggested that this is responsible for superior displacement of the terminal forces of the electrocardiogram in left ventricular hypertrophy.[8] We would agree with this hypothesis and would suggest that in the presence of a left ventricular conduction disturbance (possibly the superior division of the left bundle branch) this superior displacement might be accentuated because of delayed activation of these areas.

Three types of loops were seen in the horizontal plane. Type I was an open loop which was written entirely in a counterclockwise direction. Type II loops were somewhat narrower and had a small clockwise R tip. Type III loops were characterized by a major clockwise inscription of the R loop. A statistical comparison of Type I and Type III loops revealed that Type III loops had (a) a leftward rather than rightward Q vector, (b) more posterior R vectors of greater magnitude and delayed inscription, (c) intermediate and terminal slowing, and (d) QRS prolongation without reaching 120 milliseconds in duration. These findings suggest that Type III loops represent a stage of incomplete left bundle branch block. This hypothesis is supported by the fact that these loops are identical in contour to loops published by Gardberg and Rosen[18] during the transition from normal conduction to complete left bundle branch block in a patient with intermittent left bundle branch block. We have recently had occasion to study a similar patient with identical findings.

The incidence of loop deformity consistent with incomplete left bundle branch block was 29 per cent in the 24 cases of left ventricular hypertrophy in our series.

Cabrera and Gaxiola[4] found 4 instances of left bundle branch block in a study of 21 patients with arterial hypertension. Wood[17] found that 14 per cent of patients with severe aortic stenosis had left bundle branch block. These findings support the

concept that left bundle branch block is a frequent sequela of left ventricular hypertrophy. Conversely, Master[11] found that the majority of 90 cases of left bundle branch block studied at autopsy demonstrated left ventricular hypertrophy.

Lenègre[19] has demonstrated that complete and incomplete left bundle branch block are nearly always associated with lesions of the left bundle, usually close to its origin. Grant[7] has shown in left ventricular hypertrophy that the portion of the left ventricle that borders the aortic ring bulges into the outflow tract. Endocardial thickening and fibrosis are frequently found in this area.

The preceding facts suggest a possible mechanism for the frequent association of left bundle branch block with left ventricular hypertrophy. It is possible that, as the subaortic portion of the interventricular septum hypertrophies and bulges into the left ventricular outflow tract, it is subjected to unusual trauma. As a result of this trauma, local endocardial fibrosis occurs. Since the origin of the left bundle is located in this subaortic region, it may become involved in the fibrotic lesions, with resultant left bundle branch block.

Summary

In this report, we have presented the vectorcardiographic findings in a group of 24 adult patients with left ventricular systolic overload. The Frank lead system was used. The results indicate that left ventricular hypertrophy may be associated with significant changes in the initial, intermediate, and terminal forces of the QRS tracing. The magnitudes of the spatial Q and R vectors were increased. The terminal portion of the tracing was straight without producing an S loop. The Q vector was directed inferiorly, in contrast to normal, and the R vector was displaced posteriorly. There was delay in inscription of the R loop and QRS duration was prolonged. The above-noted alterations of the QRS loop in left ventricular hypertrophy have been discussed in relation to our present understanding of the anatomic and electrophysiologic sequelae of left ventricular enlargement.

Twenty-nine per cent of the patients in this study demonstrated loop characteristics which suggested incomplete left bundle branch block. These changes consisted of (a) leftward initial forces, (b) extreme posterior displacement and delayed inscription of the R loop, (c) clockwise rotation of the R loop in the horizontal plane, (d) intermediate or terminal slowing, and (e) QRS prolongation. The frequent association of complete and incomplete left bundle branch block with left ventricular hypertrophy was discussed and a possible mechanism to explain this association was proposed.

REFERENCES

1. Cabrera, E. C., and Monroy, J. R.: Systolic and diastolic loading of the heart. I. Physiologic and clinical data, Am. Heart J. 43:661, 1952.
2. Frank, E.: An accurate, clinically practical system for spatial vectorcardiography, Circulation 13:737, 1956.
3. Estes, E. H., Jr., McCall, B., and Wallace, A. G.: Time expansion in vectorcardiography: the advantages of magnetic tape recording, Am. Heart J. 63:98, 1962.
4. McCall, B., Wallace, A. G., and Estes, E. H., Jr.: The characteristics of the normal vectorcardiogram: a study using the Frank lead system, Am. J. Cardiol. (In press.)
5. Grant, R. P.: The relationship between the anatomic position of the heart and the electrocardiogram, Circulation 7:890, 1953.
6. Cabrera, E. C., and Gaxiola, A.: Diagnostic contributions of the vectorcardiogram in hemodynamic overloading of the heart, Am. Heart J. 60:296, 1960.
7. Grant, R. P.: Architectonics of the heart, Am. Heart J. 46:405, 1953.
8. Bryant, J. M.: In Kossmann, C. E., editor: Advances in electrocardiography, New York, 1953, Grune & Stratton, Inc., p. 159.
9. Lowe, T. E., and Bate, E. W.: The diameter of cardiac muscle fibers: a study of the diameter of cardiac muscle fibers in the left ventricle in normal hearts and in the left ventricular enlargement of simple hypertension, M. J. Australia 1:467, 1948.
10. Uhley, H. N.: Study of the transmembrane action potential, electrogram, electrocardiogram and vectorcardiogram in rats with left ventricular hypertrophy, Am. J. Cardiol. 7:211, 1961.
11. Linzbach, A.: Mikrometrische und histologische studien of cardiac hypertrophy, Virchows Arch. path. Anat. 314:534, 1947.
12. Sodi-Pallares, D.: New bases of electrocardiography, St. Louis, 1956, The C. V. Mosby Company, p. 242.
13. Bryant, J. M.: Effect of potassium on the ventricular deflections of the electrocardiogram in hypertensive cardiovascular disease, Proc. Soc. Exper. Biol. & Med. 67:557, 1948.
14. Marsolesi, A., Wolff, R., and Wolff, L.: The vectorcardiogram in left ventricular hypertrophy, Am. Heart J. 38:648, 1949.

15. Scher A. M and Young A. C. The pathway of ventricular depolarization in the dog. Circulation Res. 4:461 1956
16. Gardberg M and Rosen, I L. The electrocardiogram and vectorcardiogram in various degrees of left bundle branch block, Am. J Cardiol. 1:592, 1958.
17. Wood P. Aortic stenosis, Am. J Cardiol. 1:553 1958.
18. Master A. M The relationship between bundle branch block and cardiac enlargement Am. Heart J 20 186, 1940.
19. Lenègre, J Deglaude L., and Hazim, A. Étude clinique, électrique et anatomique d'un cas de bloc de branche, *Arch. mal. coeur* 38: 154 1945

Idiopathic hypertrophic subaortic stenosis

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Obstruction to left ventricular ejection is generally associated with a discrete stenotic area of fixed orifice size located at the aortic valve (valvular stenosis)[1] in the aorta itself just above the valve (supravalvular stenosis)[1] or immediately below the valve (subvalvular stenosis).[1] A pressure gradient from the left ventricle to the aorta is commonly assumed to reflect one of these three types of stenosis, each of which is currently amenable to corrective operation. Recently an additional type has been described—idiopathic hypertrophic subaortic stenosis[2,3]—which is characterized by a left ventriculo-aortic gradient in the absence of discrete anatomic obstruction. In this malformation resistance to ejection is caused by systolic narrowing of an area of diffuse muscular hypertrophy in the left ventricular outflow tract. The degree of obstruction varies directly with the force of ventricular contraction (nonfixed orifice size) an observation that has led to the development of a simple hemodynamic method for the detection of this lesion.[4] Since a satisfactory technique for its surgical correction has not yet been developed differentiation from other types of aortic stenosis is imperative.

The purpose of this report is to present clinical and hemodynamic information in an additional case of idiopathic hypertrophic subaortic stenosis. These data are considered to be of value because of the limited number of published descriptions because of the need to recognize the malformation in order to avoid unnecessary operation and because of our confirmation of the recently described hemodynamic method for its diagnosis.

Case report

The patient, a 30-year-old white woman, entered Georgetown University Hospital for evaluation of a cardiac murmur which had first been discovered when she was 26 years old. Except for dyspnea with severe effort there were no convincing cardiac symptoms, and no medications were being taken. She was born of a normal full-term pregnancy. Examination during childhood did not disclose evidence of a congenital malformation. There was no history of rheumatic fever or of arterial hypertension. The father died at the age of 61 of coronary artery disease. The family history was otherwise negative. The patient had experienced two asymptomatic pregnancies, each of which ended in second trimester spontaneous abortions. Review of systems was noncontributory.

Physical examination. The patient was a well-developed white woman who appeared to be in good health. Blood pressure in the right arm was 115/80 mm. Hg and in the left arm, 110/70 mm. Hg. The cardiac rate was 80 per minute, and the rhythm was regular with a sinus arrhythmia. Palpation of the brachial, femoral, and carotid arteries

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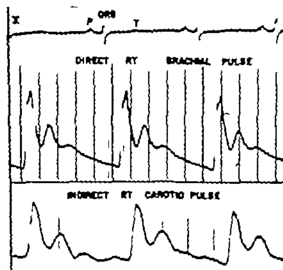


Fig. 1. The tracings emphasize the similarity between direct and indirect recordings, and illustrate the rapid rate of rise and systolic trough seen in the systemic arterial pressure pulse.

revealed quick rising pulses (Fig. 1). The *A* and *V* waves of the jugular venous pulse were normal in height and contour. There was a mild pectus excavatum. The lungs were normal to percussion and auscultation. Palpation of the precordium revealed a moderately dynamic left ventricular lift between the mid-clavicular and anterior axillary lines and a systolic thrill in the same area. The right ventricle was not palpable. No thrills were felt at the base, in the suprasternal notch, or over the carotid arteries. Auscultation of the heart (Fig. 2) disclosed a Grade 4 (out of Grades 1-6) ejection type systolic murmur which was loudest at the lower left sternal edge and apex, and which radiated with progressively diminishing intensity toward the base and axilla. Careful auscultation in the second right intercostal space and along the left sternal border failed to detect the murmur of aortic regurgitation. The first heart sound was normal at all areas, and an aortic ejection sound was not heard. At the upper left sternal edge, the second heart sound split narrowly on inspiration into aortic and pulmonic components, but on some occasions paradoxical splitting was suspected. At the apex, the first heart sound was preceded by an atrial sound, and the second sound was followed by a soft third heart sound. The remainder of the physical examination was normal. The urinalysis, total and differential white blood cell counts, hematocrit, hemoglobin, blood urea nitrogen, fasting blood sugar, serologic test for syphilis, and coagulation studies were all normal. The electrocardiogram (Fig. 3) was interpreted as indicating left axis deviation and left ventricular hypertrophy with a loss of anteriorly directed QRS electrical forces manifested by QS waves in Leads V_1 through V_4. Chest x-ray films in the posteroanterior and oblique views (Fig. 4) revealed left ventricular enlargement with no dilatation of the aortic root, no calcium in the aortic valve, and no evidence of displacement of the barium-filled esophagus by a large left atrium.

In the Catheterization Laboratory the right brachial arterial pulse was photographically recorded simultaneously with the left ventricular pulse, which was obtained by percutaneous puncture, using the subxyphoid approach (Fig. 5). Care was taken to record a suitable number of premature ventricular contractions, including beats following the compensatory pauses. The cardiac output was

Table I. Physiologic data

Position	Pressures				
	Systolic	*Diastolic*	*Mean*	*Peak systolic gradient*	*Mean systolic gradient*
Right ventricle	36	2–10			
Left ventricle	160–166	16–20			
Brachial artery	118–140	50–64	82		
Gradient				25–70	20–36

Cardiac output—6 07 L./min.
Cardiac index—3.80 L./min./M.²
Stenotic orifice area—Inspiration 1.41 cm.², expiration 0.7 cm.²
Brachial arterial pulse—Rate of rise 1,200 mm. Hg/sec.
Onset to peak 0.09 sec.
Onset to dicrotic notch 0.31 sec.
Total systemic vascular resistance—1,079 dynes sec. cm.⁻⁵
Effective left ventricular minute work index—4.46 Kg.M./M.²
Effective left ventricular stroke work index—61 Gm.M./M.²
Left ventricular minute work index—5.7 Kg.M./M.²
Left ventricular stroke work index—79 Gm.M./M.²

determined in duplicate by the indicator-dilution method, using the peripheral venous injection technique of Fox. Indocyanine green was injected from calibrated syringes into the left median basilic vein. Sampling was performed from the right brachial artery using a constant withdrawal syringe through a Gilford cuvette densitometer. The results are summarized in Table 1.

Discussion

The concept of left ventricular outflow obstruction has been broadened to include a category of stenosis caused by systolic contraction of an area of diffuse subvalvular muscular hypertrophy. Since the hypertrophy is not secondary to any known stimulus, the disorder has been designated "idiopathic hypertrophic subaortic stenosis."[2] Although the number of reported cases is limited, the clinical, physiologic, and pathologic similarities presumptively identify them as a distinct disease state. In 1958 Bercu and associates[6] described a patient with a harsh systolic murmur and thrill between the apex and left sternal border, with radiologic and electrocardiographic evidence of left ventricular enlargement, and with a left ventriculo-aortic gradient of 130 mm. Hg. In spite of the atypical location of the murmur and thrill, the gradient was considered to be diagnostic of aortic stenosis. At open-heart operation no discrete area of obstruction was encountered. Post-mortem examination revealed remarkable myocardial hypertrophy, which the authors believed to be the cause of the gradient. There was additional evidence that this curious disorder may have been heredofamilial. In 1959 three additional reports appeared from independent sources. Brock[7] called attention to 5 cases in which ventricular hypertrophy was associated with

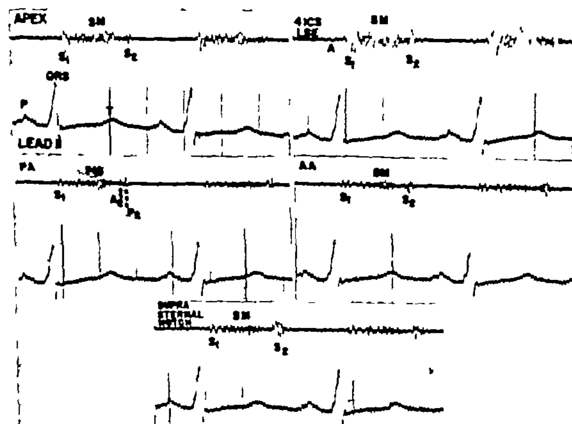


Fig. 2. Logarithmic phonocardiograms recorded at the cardiac apex, fourth intercostal space left sternal edge (*4 ICS, LSE*), pulmonary area (*PA*), aortic area (*AA*), and in the suprasternal notch. S_1, First heart sound. S_2, Second heart sound. A_2, Aortic component of the second heart sound. P_2, Pulmonic component of the second heart sound. *A*, Atrial sound. *SM*, Systolic murmur.

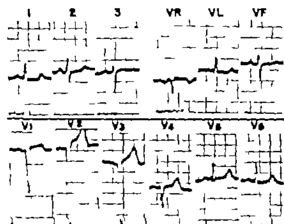


Fig. 3. Twelve-lead scalar electrocardiogram. Leads V4 through V6 are half standardized.

functional obstruction to left ventricular ejection. Morrow and Braunwald[2] described 2 patients with hemodynamic evidence of resistance to left ventricular outflow but without detectable anatomic obstruction at operation. Soulié and associates described 2 similar cases in which marked hypertrophy caused diffuse stenosis of the entire outflow tract of the left ventricle. Emphasis was placed on the peculiar configuration of the systolic arterial pressure pulse. In contrast to the configuration in typical valvular or subvalvular aortic stenosis, the ascending limb of the pulse was rapid with a secondary fall which corresponded to the production of obstruction by the contracting left ventricular outflow tract. In Brachfeld and Gorlin's[9] discussion of subaortic stenosis, 2 patients appeared to fall into the group in which myocardial hypertrophy was evidently the basic cause of impediment to left ventricular ejection. In 1960 Brent and associates[10] described 3 patients with proved muscular subaortic stenosis. Clinical findings strongly suggested at least 3 additional cases in one family and 5 in the other. Studies of the pedigrees revealed evidence of an heredofamilial disorder transmitted as a Mendelian dominant. More recently Braunwald and associates[3] comprehensively reviewed the clinical, hemodynamic, and angiocardiographic manifestations in 14 new cases of idiopathic hypertrophic subaortic stenosis and shortly thereafter described a simple hemodynamic technique for its detection.[4] Analysis of this group of patients indicated that the malformation may be familial but not congenital, may be congenital but not familial, or may be present in adult life as neither congenital nor familial. Daoud's[11] case of obstructive ventricular hypertrophy ("muscular subaortic stenosis") occurred in a 1 year-old child and hence is of additional interest since it represents the youngest patient thus far described in this category.

Taken together, the historical, physical, electrocardiographic, and radiologic features of idiopathic hypertrophic subaortic stenosis permitted clinical recognition in our case so that the proper hemodynamic



Fig. 4. Chest roentgenograms in the right anterior oblique, posteroanterior, and left anterior oblique projections.

technique for its confirmation could be selected.

History. The patient may be asymptomatic or may experience arrhythmias, easy fatigability, congestive heart failure, angina, syncope, or sudden death.[3] In view of the observations that an augmented force of ventricular contraction *increases* the degree of stenosis,[4] it has been suggested that drugs with a positive inotropic effect should be used with caution.[4] Therefore, it has been postulated that symptomatic deterioration after the administration of digitalis may be an historical feature to arouse suspicion of idiopathic hypertrophic subaortic stenosis.[11b]

Physical signs. The physical examination does not yield classic evidence of aortic stenosis. The peripheral arterial pulse is either normal or actually quick rising (Fig. 1). Palpation of the precordium reveals a dynamic left ventricular lift. A systolic thrill is felt not in the second right intercostal space or in the neck but, instead, between the apex and lower left sternal border. A loud, harsh systolic murmur is best appreciated in the same region and is generally not well heard in the aortic area or over the carotid arteries (Fig. 2). Although these physical signs suggest mitral insufficiency or ventricular septal defect, further analysis of the auscultatory features should permit the correct diagnosis to be suspected. The murmur may be ejection in type.[3] This configuration together with a palpable left ventricle directs attention to the aortic valve as the site of origin of the bruit. A prominent atrial sound is usually heard, an acoustic event that is common in idiopathic hypertrophic subaortic stenosis[3] but infrequent in uncomplicated mitral insufficiency[12] or ventricular septal defect.[13] A third heart sound (ventricular diastolic gallop) can also be present. Analysis of the second heart sound may reflect a prolonged duration of left ventricular ejection and consequently a delay in closure of the aortic valve which results in either a single second heart sound or, in the more severe cases, paradoxical splitting.[14] In uncomplicated ventricular septal defect[15] and in mitral insufficiency[12] the second heart sound is rarely single and the sequence of closure of the semilunar valves is always normal. Thus far an aortic ejection sound or the blowing decrescendo diastolic murmur of aortic insufficiency have not been reported in idiopathic hypertrophic subaortic stenosis.[3] The diagnosis of this malformation should therefore be questioned if these latter two signs are present. In some cases, coexisting mitral insufficiency results in an apical pansystolic murmur, making the diagnosis more difficult.[3]

Electrocardiogram. The electrocardiogram generally shows left ventricular hypertrophy and occasionally evidence of left

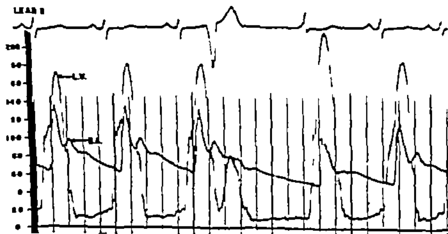


Fig. 3. Simultaneously recorded electrocardiogram (*Lead II*), left ventricular pulse (*L.V.*), and brachial arterial pulse (*B.A.*), illustrating the fall in brachial arterial pulse pressure in the beat after the premature contraction.

atrial enlargement In our case there was *in addition left axis deviation and the* QS deformities in Leads V_1 through V_3. The anomalous atrioventricular excitation reported in 4 cases[3] is a feature of additional interest.

X ray examination. Radiologic examination[3,7] reveals evidence of concentric hypertrophy of the left ventricle but calcification of the aortic valve and poststenotic dilatation of the aorta are conspicuous by their absence The left atrium may also be enlarged especially when there is coexisting mitral insufficiency

The *features which should permit clinical* suspicion of idiopathic hypertrophic subaortic stenosis might be summarized as follows. The patient presents for evaluation of a murmur which has usually been diagnosed as mitral insufficiency or perhaps ventricular septal defect but without a history of rheumatic fever and often without a history of a murmur in the first years of life There may be evidence of a familial incidence of heart disease and the patient may report symptomatic deterioration after administration of *italis.*[11b] *Physical examination reveals a* quick rising arterial pulse a thrill and a loud ejection or pansystolic murmur between the cardiac apex and the lower left sternal edge There is a prominent atrial sound and a second heart sound that is likely to be single or even paradoxically split An ejection sound is unlikely and the murmur of aortic insufficiency is not heard The *electrocardiogram and x ray* films reveal left ventricular hypertrophy but calcification of the aortic valve and dilatation of the ascending aorta are conspicuously absent

Retrograde catheterization of the left ventricle allows the localization of subvalvular stenosis,[4] but does not distinguish the discrete fixed orifice type of obstruction from idiopathic hypertrophic subaortic stenosis. In patients with the latter malformation selective left ventricular angiography constitutes a valuable diagnostic technique[3] by demonstrating systolic narrowing and diastolic relaxation of the outflow tract The angiocardiographic evidence that a decrease in orifice size results from myocardial contraction led Brockenbrough and associates[4] to postulate an inverse relationship between the force of ventricular *systole and the effective size of the stenotic* area thereby formulating the basis of a simple hemodynamic method for the detection of idiopathic hypertrophic subaortic stenosis. The longer diastolic filling period after a premature ventricular beat results in increased contractile force of the compensatory beat This augmented strength of contraction is associated with a decrease in orifice size and hence a fall in the arterial pulse pressure In aortic stenosis with fixed obstruction to left ventricular outflow the orifice remains unchanged *permitting an increase in arterial pulse* pressure during the compensatory beat. In our case a deliberate effort was made to induce and record premature ventricular beats and their compensatory pauses. Analysis of these tracings indicated that the arterial pulse pressure varied inversely with the left ventricular systolic pressure and with the duration of the preceding diastole thus diagnosing idiopathic hypertrophic subaortic stenosis.[4] In addition the cycle lengths and hence the diastolic filling periods varied continually because of a *marked sinus arrhythmia During inspiration* the cardiac rate accelerated the diastolic filling period shortened the arterial pulse pressure increased and the calculated orifice size was 1 4 sq cm On the other hand during expiration the cardiac rate slowed the filling period lengthened the arterial pulse pressure decreased and the calculated orifice size was 0 7 sq cm These *observations support the suggestion*[3,4] *that* beat to-beat variations in the size of the left ventricular outflow tract occur in idiopathic hypertrophic subaortic stenosis.

The contours of the left ventricular and arterial pressure pulses deserve further comment (Fig 5) During early systole ejection is rapid and the brachial pulse rises virtually in parallel with the ventricular The ascending *limb of the left ventricular* pulse (recorded proximal to the *obstruction) then exhibits a notch or slur*[4] At this point the area of subvalvular hypertrophy probably begins to contract allowing the arterial pressure momentarily to exceed the ventricular With rapid progressive systolic narrowing of the orifice the left ventricular pressure continues to rise but *the arterial pressure falls abruptly*

resulting in a pronounced mid-systolic trough followed by a secondary rise and a gradual fall to the dicrotic notch. The diagnostic significance of the unusual contour of the arterial pulse bears emphasis.[1,10,11,14] Its reflection in the indirect carotid pulse[1] (Fig 1) and its value as a physical sign[10] have been commented upon. It must be pointed out however that this contour has not been recorded in all cases of idiopathic hypertrophic subaortic stenosis.[10,11]

There is evidence that the left ventricular hypertrophy in this malformation precedes the development of the gradient and indeed is its fundamental cause. Thus three relatives of propositi reported on by Braunwald and associates[3] had prominent left ventricular lifts, harsh systolic murmurs at the left sternal border and radiologic signs of left ventricular enlargement, but no systolic gradients were detected. Pertinent to the considerations of etiology are the cases of familial cardiomegaly [10,15] and of asymmetrical hypertrophy of the heart[17] which might conceivably result in left ventricular outflow obstruction. Indeed Goodwin and associates[16] described clinical and hemodynamic findings in a patient with obstructive cardiomyopathy simulating aortic stenosis, and at operation obstruction of the outflow tract was attributed to enormous hypertrophy of the ventricular septum (asymmetrical hypertrophy of the heart) It is of interest that this patient had an aortic ejection sound These authors also presented data on 7 additional patients in whom they believed that left ventricular hypertrophy of unknown etiology caused obstruction to outflow Although hemodynamic data were not described in Paré's study of hereditary cardiomegaly [15] the configuration and location of the systolic murmurs, the presence of atrial sounds, the electrocardiographic evidence of left ventricular hypertrophy and the contour of the brachial arterial pressure pulses strongly suggest that the report included cases of idiopathic hypertrophic subaortic stenosis. It is of considerable interest that there were examples of both diffuse and asymmetrical hypertrophy in different members of the same family

An alternative etiological hypothesis suggested to one of us (J.K.P.) by Dr M G Criscitiello* proposed that obstruction to left ventricular outflow may be caused by an abnormal sequence of contraction of the major structural units of the ventricular muscle. In 1927 Flett[18] emphasized that the deep bulbospiral muscle—a powerful sphincter which encircles the left ventricular base—must contract later than the other muscle fibers. In 1942 Robb and Robb[19] further elaborated "If the deep bulbospiral contracted early it would produce narrowing of the aortic outlet and this would be equivalent to aortic stenosis. Since it contracts late it completes the emptying of the ventricle supports the column of blood in the aorta and when it relaxes, the aortic valves fall back into position and maintain the diastolic pressure. It is entirely possible that more than one causative factor contributes to the development of idiopathic hypertrophic subaortic stenosis.

Evidence indicates that diffuse subvalvular hypertrophy may occur in response to a known resistance to left ventricular ejection Thus, it has been described with pre-existing systemic hypertension [20] and with valvular or discrete subvalvular aortic stenosis.[3,4] Cases in these latter categories in which the etiology seems to be apparent might be designated as "secondary hypertrophic subaortic stenosis"[3] whereas cases without antecedent resistance to left ventricular ejection—represented by the patient herein reported—might be designated as primary or idiopathic hypertrophic subaortic stenosis according to the recommendation of Braunwald and associates.[3]

Both of these types of stenosis appear to have their parallels on the right side of the heart. Secondary obstruction to right ventricular outflow may develop as a sequel of valvular pulmonic stenosis[21] or of pulmonary hypertension associated with ventricular septal defect.[22] Patients with idiopathic hypertrophic subaortic stenosis may also have a gradient across the right ventricular outflow tract,[3,4,11] and Rodbard and associates[23] described a type of subvalvular pulmonic stenosis in which the orifice appeared to narrow as a result of

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right ventricular contraction. Simultaneous recordings of right ventricular and pulmonary arterial pressure pulses in these cases bear impressive similarities in contour to the left ventricular systemic arterial pulses in idiopathic hypertrophic subaortic stenosis (Fig. 1).[3,4,16]

Clinical recognition and hemodynamic confirmation of this malformation are essential in preventing patients from being operated upon because they are thought to have the fixed orifice types of aortic stenosis. Indeed many cases were initially discovered when the surgeon failed to detect a discrete area of obstruction.[2,4,9,11] Although a surgical technique for the relief of idiopathic hypertrophic subaortic stenosis has been employed with encouraging initial results,[1] it would seem appropriate to emphasize that selection for this operation should be made in only the more severe cases until the ultimate value of the operation has been properly assessed.

Summary

The clinical and hemodynamic features of a case of idiopathic hypertrophic subaortic stenosis are presented. Criteria for its clinical recognition are assessed and current concepts of its pathophysiology are briefly reviewed with confirmation of a recently described technique for its hemodynamic detection. The importance of separating cases in this category from those in the categories of aortic stenosis which are amenable to corrective operation is emphasized.

REFERENCES

1 Brock, R. C.: Differentiation of valvular, subvalvular and supravalvular aortic stenosis. Guy's Hosp. Rep. 110:1 1961.
2 Morrow, A. G., and Braunwald, E.: Functional aortic stenosis. Circulation 20:181 1959.
3 Braunwald, E., Morrow, A. G., Cornell, W. P., Aygen, M. M., and Hilbish, T. F.: Idiopathic hypertrophic subaortic stenosis. Clinical hemodynamic and angiographic manifestation. Am. J. Med. 29:924 1960.
4 Brockenbrough, E. C., Braunwald, E., and Morrow, A. G.: A hemodynamic technique for the detection of idiopathic hypertrophic subaortic stenosis. Circulation 23:189 1961.
5 Fox, Samuel III: Personal communication.
6 Bercu, B. A., Diettert, G. A., Danforth, W. H., Pund, E. E., Jr., Ahlvin, R. C., and Belliveau, R. R.: Pseudoaortic stenosis produced by ventricular hypertrophy. Am. J. Med. 25:814 1958.
7 Brock, R. C.: Functional obstruction of the left ventricle. Guy's Hosp. Rep. 108:126, 1959.
8 Soulié, P., Degeorges, M., Joly, F., Carlamaulin, M., and Carlotti, J.: A source of error in the hemodynamic diagnosis of aortic stenosis. Arch. mal. coeur 9:1002 1959.
9 Brachfeld, N., and Gorlin, R.: Subaortic stenosis, Medicine 38:415 1959.
10 Brent, L. B., Aburano, A., Fisher, D. L., Moran, T. J., Myers, J. D., and Taylor, W. J.: Familial muscular subaortic stenosis, Circulation 21:167 1960.
11a Daoud, G., C. Baker, M. F., and Kaplan, S.: Muscular subaortic stenosis, Am. J. Cardiol. 7:800 1961.
11b Braunwald, E., Brockenbrough, E. C., and Frye, R. L.: Studies on digitalis. V. A comparison of the effects of ouabain on left ventricular dynamics in valvular aortic stenosis and hypertrophic subaortic stenosis, Circulation (In press).
12 Brigden, W., and Leatham, A.: Mitral incompetence. Brit. Heart J. 15:55 1953.
13 Wood, P., Magidson, O., and Wilson, P. A. O.: Ventricular septal defect with a note on acyanotic Fallot's tetralogy. Brit. Heart J. 16:387 1954.
14 Gray, I.: Paradoxical splitting of the second heart sound. Brit. Heart J. 18:21 1956.
15 Paré, J. A. P., Fraser, R. G., Pirozynski, W. J., Shanks, J. A., and Stubington, D.: Hereditary cardiovascular dysplasia. Am. J. Med. 31:37 1961.
16 Goodwin, J. F., Hollman, A., Cleland, W. P., and Teare, D.: Obstructive cardiomyopathy simulating aortic stenosis. Brit. Heart J. 22:403 1960.
17 Teare, D.: Asymmetrical hypertrophy of the heart in young adults. Brit. Heart J. 20:1 1958.
18 Mall, F. P.: The musculature of the heart and its application to physiology and a note on heart rupture. J. Anat. 68:139 1927.
19 Robb, J. S., and Robb, R. C.: The normal heart. Am. Heart J. 23:455 1942.
20 Brock, R. C.: Functional obstruction of the left ventricle. Guy's Hosp. Rep. 106:221 1957.
21 Rothard, S., and Schaffer, A. B.: Muscular contraction in the infundibular region as mechanism of pulmonic stenosis in man. Am. Heart J. 51:885 1956.
22 Gasul, B. M., Dillon, R. F., Vrla, V., and Hait, G.: Ventricular septal defects. Their natural transformation into those with infundibular stenosis or into the cyanotic or noncyanotic type of tetralogy of Fallot. J.A.M.A. 164:847 1957.

Delay in the onset of right ventricular contraction in patients with surgically induced disturbance of right ventricular conduction

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It is now clear that electrocardiographic evidence of a disturbance in right ventricular conduction with QRS prolongation develops in the majority of patients in whom an isolated ventricular septal defect is repaired or in whom the tetralogy of Fallot is completely corrected.[1-4] The etiology of this abnormality of ventricular depolarization has been attributed to surgical trauma to the right bundle branch[1] or to a parietal block resulting from an incision in the free wall of the right ventricle[7] or in the crista supraventricularis.[1]

Substantial evidence has accumulated which links anatomic lesions in the main right bundle branch with the electrocardiographic configuration of right bundle branch block, and with a delay in the onset of right ventricular contraction. For example, it has been shown that, when the right bundle branch is surgically interrupted in experimental animals, the prolongation of the QRS complex is accompanied by a delay in the onset of right ventricular contraction.[4-6] In detailed pathologic studies on patients who had electrocardiographic evidence of right bundle branch block, significant lesions of the conduction system have been demonstrated consistently.[7] It has also been shown that the time interval between the onset of depolarization and of right ventricular contraction is prolonged in patients with the electrocardiographic configuration of complete right bundle branch block, presumably on a congenital basis.[8,9] However, there was no delay in the onset of right ventricular contraction in the majority of patients with right ventricular enlargement accompanied by the electrocardiographic findings of right bundle branch block.[10] Vectorcardiographic studies in the latter patients have supported the view that the disturbance in ventricular activation is not related to a block in conduction of the main right bundle branch.[8]

It was reasoned, therefore, that, if the right ventricular conduction disturbance which develops after repair of a ventricular septal defect is caused by interference with conduction in the right bundle branch, it

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should be accompanied by a delay in the onset of right ventricular contraction If on the other hand these alterations in the electrocardiogram are secondary to an abnormality of depolarization which involves only a segment of the right ventricle as in parietal block which results from the ventriculotomy then the onset of contraction of the major portion of the right ventricle should occur at a normal time. It was the objective of this study to elucidate the mechanism of this postoperative prolongation of the QRS complex by comparing the preoperative and postoperative time intervals between the onset of ventricular depolarization and of right ventricular contraction

Patients and methods

The data for this study were obtained on 17 patients who ranged in age from 7 to 30 years (average of 12 years) The patients were selected by the following criteria (1) All were operated upon for closure of a ventricular septal defect This was an isolated lesion in 11 of the and formed a part of the tetralogy allot in the other 6. (2) The electro-ographic features of right bundle anch block were not present prior to operation they developed during the operation and were still present at the time of the postoperative cardiac catheterization. Patients were included only if (a) the QRS duration before operation did not exceed 0 10 sec (b) the postoperative QRS duration was 0 12 sec or longer (c) the prolongation of the QRS duration induced by operation was at least 0 03 sec (Fig 1) and (d) in the postoperative electrocardiogram the configuration of the QRS complex in the right precordial leads demonstrated a delayed intrinsicoid deflection of the R or R wave. (3) All patients had been studied by catheterization of the right side of the heart both before and after operation The latter studies were carried out 6 to 12 months postoperatively (4) The pressure tracings obtained at catheterization permitted measurement of the time intervals between the onset of ventricular depolarization and the onset of right ventricular contraction with an accuracy of at least 0 01 sec

All 17 patients were operated upon with the aid of total cardiopulmonary bypass, and a rotating disc oxygenator was used In the 11 patients with isolated ventricular septal defects a vertical right ventriculotomy was made and the defect was closed by direct suture in 5 and by means of a Teflon or Ivalon patch in the other 6 In the 6 patients with tetralogy of Fallot the ventricular septal defects were repaired by direct suture in 2 and by a patch in 4 an infundibular resection was then performed and in 4 of the patients the right ventricular outflow tract was also enlarged by means of a prosthetic device.

At cardiac catheterization Lead II of the electrocardiogram was recorded simultaneously with the right ventricular pressure pulse. In general the recordings were made with a multichannel photographic oscilloscopic instrument, and in a few instances, with a direct writing instrument The time intervals between the onset of QRS and of right ventricular contraction which are presented below were the average measurements obtained from several cardiac cycles 0 01 sec was subtracted from the measured time intervals to account for the delay in the transmission of the pressure pulse imposed by the catheter and the connecting tubing[15]

Results

A comparison of the QRS durations prior to operation and at the time of postoperative catheterization are presented in Fig 1 Preoperatively the QRS durations in Lead II ranged from 0 04 to 0 10 sec with an average duration of 0 079 sec Postoperatively the durations ranged from 0 12 to 0 16 sec. with an average of 0 127 sec. The increase in QRS duration in the individual patients ranged from 0 03 to 0 08 sec. with a mean value of 0 048 sec.

The relationships between QRS duration and the time intervals between the onset of ventricular depolarization and the onset of right ventricular contraction (Q RV) are shown in Fig 2 Preoperatively Q-RV was within normal limits (up to 0 08 sec.) in 15 of the 17 patients, and minimally prolonged (0 09 sec) in the other 2 patients. After the operation Q-RV became abnormally prolonged (0.10 sec. or longer)

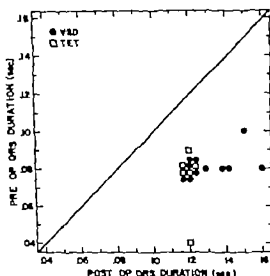


Fig. 1 Comparison of preoperative and postoperative QRS durations in the 17 patients studied.

in 9 patients, was minimally prolonged (0.09 sec.) in 5 patients, and remained within normal limits in the other 3 patients. When the Q-RV interval in the tracings obtained before operation was compared with that in the tracings obtained after operation we observed that it had increased by 0.02 to 0.06 sec. in 11 patients. This time interval increased by 0.01 sec in 3 patients and remained unchanged in the other 3 patients. A representative right ventricular pressure tracing which was obtained in the postoperative period and which demonstrates an abnormally prolonged Q-RV interval is reproduced in Fig 3

Discussion

As indicated above, the only patients included in this study were those in whom electrocardiographic evidence of a right ventricular conduction disturbance developed during operation and persisted during the postoperative period. In 11 of the 17 patients studied the development of this electrocardiographic configuration was accompanied by a prolongation of the Q-RV interval which was significant when compared with the preoperative measurement in 9 of the patients studied postoperatively this time interval was sig

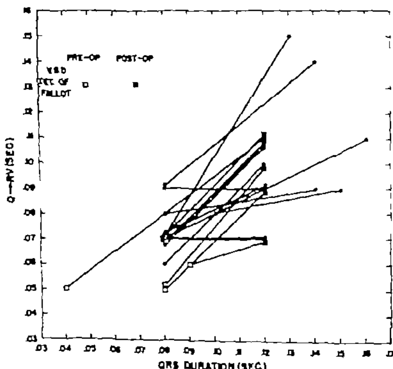


Fig 2. Relationship between QRS duration and the time interval between Q and the onset of right ventricular contraction (Q-RV) preoperatively and postoperatively

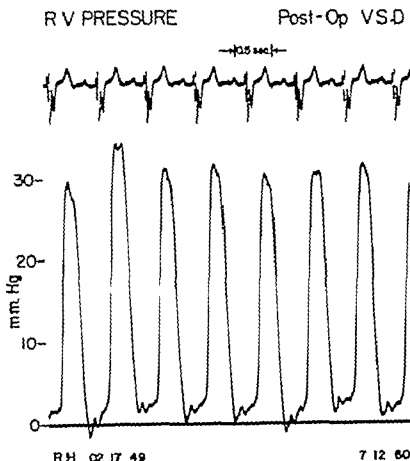


Fig. 3. Simultaneous electrocardiogram and right ventricular (R.V.) pressure pulse in a patient after closure of a ventricular septal defect (V.S.D.). The electrocardiographic configuration of right bundle branch block is evident and there is abnormal prolongation of the interval between Q and the onset of right ventricular contraction. Paper speed, 25 mm. per second.

nificantly prolonged when compared with normal values. The slight prolongation of Q-RV which occurred in several of the other patients is of questionable significance. However, it is pertinent that Q-RV did not change in 3 patients in spite of the development of the electrocardiographic configuration of right bundle branch block.

We concluded from these observations that a mechanical delay in the onset of right ventricular contraction develops in the majority of patients with ventricular septal defect and tetralogy of Fallot with electrocardiographic findings of a right ventricular conduction disturbance in the postoperative period. It would seem unlikely that such a significant delay in the onset of right ventricular contraction could occur without a delay in depolarization of all or a major portion of the right ventricular myocardium. Complete interruption of or significant trauma to the main right bundle branch would best explain the development of this mechanical delay.

On the other hand, it appears that in those few patients who developed electrocardiographic evidence of a right ventricular conduction disturbance and in whom a mechanical delay in the onset of right ventricular contraction did not occur, the prolongation of the QRS is related to a peripheral disturbance in ventricular activation without injury to the main right bundle branch. Coggin and Selvester[8] have observed that the electrocardiographic development of "atypical right bundle branch block" occurred when the right ventricle was incised and before sutures

were placed into the ventricular septum i.e., presumably before the right bundle branch could have been traumatized surgically. These observations were also confirmed in experimental animals. However in that investigation the time intervals between ventricular depolarization and ventricular contraction were not measured. Thus, it seems likely that the electrocardiographic findings of "right bundle branch block" will develop in almost all of the patients in whom a right ventriculotomy is performed. This will not be accompanied by a delay in the onset of right ventricular contraction unless, in addition the right bundle branch is injured. When one considers the anatomic proximity of the posterior inferior margin of ventricular septal defects to the right bundle branch[1] the frequency of trauma to this structure during the operative repair of a ventricular septal defect is understandable.

The delay in the onset of right ventricular contraction after repair of a ventricular septal defect may assume clinical significance from at least four points of view. First of all the asynchronous contraction of the two ventricles may be responsible for the development of the wide splitting of the first and second heart sounds which is common in these patients. Second the delay in the onset of right ventricular contraction is accompanied by prolongation of right ventricular ejection; this may result in reversal of the pressure gradient between the ventricles in late systole, after left ventricular pressure has begun to decline. This evidently occurred in 2 of our patients in whom the defect could not be completely closed and who developed arterial unsaturation after operation even though the peak systolic pressures in the left ventricles exceeded that in the right ventricles by 30 mm Hg. Third the delay in the onset of right ventricular contraction augments the pressure differential between the two ventricles, i.e. during very early systole the left ventricular pressure is unopposed by right ventricular pressure, and the reverse occurs at the end of ventricular systole. This raises the mechanical stress placed on the closed defect and perhaps increases the possibility of its reopening. Finally if the right bundle branch is interrupted the normal sequence of right ventricular activation is disturbed and the normal sequence of fractionate contractions is altered.[15] The latter may in turn impair right ventricular contractility[12] and this could assume clinical importance particularly in the early postoperative period.

Summary

In this study we attempted to elucidate the mechanism responsible for the electrocardiographic evidence of right ventricular conduction disturbance which develops in patients after surgical closure of ventricular septal defects and repair of the tetralogy of Fallot. The time intervals between the onset of ventricular depolarization and of right ventricular contraction were determined both before and after operation in 17 patients who developed this electrocardiographic abnormality. In 11 of the 17 patients the time interval increased by 0.02 to 0.06 sec, in 3 patients it increased by 0.01 sec, and it remained unchanged in the other 3 patients. We have concluded that the mechanical delay in the onset of right ventricular contraction which develops in the majority of patients after closure of ventricular septal defects and complete correction of the tetralogy of Fallot results from interruption of or other trauma to the right bundle branch.

REFERENCES

1. Zimmerman, H. A., Martins de Oliveira, J., Nogueira, C., Mendelsohn, D., and Kay, E. B.: Electrocardiogram in open-heart surgery. Disturbances in right ventricular conduction. J. Thoracic Surg. 36:12, 1958.
2. Coggia, C. J., and Schroeter, R. H.: Post ventriculotomy electrocardiogram and vectorcardiogram: a preliminary report. M. Arts & Sc. 13:161, 1959.
3. Dickens, J., Maranhao, V., and Goldberg, H.: Right bundle branch block: a vectorcardiographic and electrocardiographic study of ventricular septal defect following open heart surgery. Circulation 20:201, 1959.
4. Bristow, J. D., Kassebaum, D. G., Starr, A., and Griswold, H. E.: Observations on the occurrence of right bundle branch block following open repair of ventricular septal defects. Circulation 22:896, 1960.
5. Braun-Menendez, E., and Solari, L. A.: Ventricular asynchronism in bundle branch block. Arch. Int. Med. 63:830, 1939.
6. Folli, G., Viola, E., Battioni, G. G., and Zocche, G. P.: Ventricular mechanics and intracardiac

electrocardiogram in experimental bundle branch block, Brit. Heart J 22:463 1960.
7 Lev M., Unger P N., Lesser M. E., and Pick, A. Pathology of the conduction system in acquired heart disease complete right bundle branch block, Am. Heart J 61:593 1961
8. Braunwald, E., Donoso, E., Sapin, S. O., and Grishman, A. Right bundle branch block. Hemodynamic, vectorcardiographic and electrocardiographic observations, Circulation 13:866, 1956
9 Braunwald, E., and Morrow A. G The sequence of ventricular contraction in human bundle branch block, Am. J Med. 23:205, 1957
10. Gordon, A. G., Braunwald, E., Moscovitz, H. L., and Amram, S. S. Delay in transmission of a pressure impulse through a cardiac catheter and vinyl plastic tubing, J Appl. Physiol. 8:573 1956.
11 Truex, R. C., and Bishop, J K.: Conduction system in human hearts with ventricular septal defects, J Thoracic Surg 35:421 1958.
12. Wiggers, C. J The muscular reactions of the mammalian ventricle to artificial surface stimuli, Am. J Physiol. 73:346, 1925.
13 Linden, R. J., Mitchell, J., Gilmore, J P., Brockman, S. K., and Sarnoff S. J Hemodynamic changes induced by ventricular stimulation (abstract) Fed. Proc. 18:93 1959

Myocardial fat infiltration

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It is the purpose of this paper to analyze myocardial fat infiltration in terms of cardiovascular disease in general and to describe its relative frequency in myocardial disease per se. Salient questions concern the role of myocardial fat in myocardial infarction myocardial fibrosis, cardiac rupture, and sudden unexplained death.

Myocardial fat infiltration is an uncommon autopsy finding with an over-all incidence of approximately 3 per cent. Its association with other types of myocardial disease may be incidental in some cases, but in others it appears to be an integral part of the degenerative process. The role of myocardial fat in cardiac dilatation and congestive heart failure was, in fact the original unanswered question that prompted this study

Material

A survey of the autopsy material collected in our institution between 1955 and 1960 (1 647 cases) revealed 52 cases of myocardial fat infiltration. The age distribution of the patients was between the sixth and eighth decades, inclusive. Each case used in this study was reviewed to confirm the original diagnosis. For the purpose of statistical comparison 52 cases of no myocardial fat infiltration were selected according to the age of the patients and divided by sex and the presence or absence of myocardial fibrosis. The latter diagnosis characterizes those hearts with more than a minimal degree of coronary artery atherosclerosis, and with small areas of old myocardial fibrosis, the morphologic result of long standing coronary insufficiency Cases of myocardial disease judged to be of less than 3 months duration were excluded. Cases of myocardial fat infiltration were likewise divided according to the age and sex of the patients and the concomitant presence of myocardial fibrosis. Only those cases in which fat was easily demonstrable in at least the outer one fourth of the myocardial thickness were included in the experimental group in two thirds of these cases there was fat in deeper layers of the myocardium as well Select cases of a maximum degree of fat infiltration were studied by camera lucida drawings to determine the percentage of fat infiltration in representative sections of the myocardium.

Anatomic findings

The gross picture of advanced myocardial fat infiltration is illustrated in Fig 1 Fat is easily seen in the wall of the right ventricle and beneath the endocardium of the trabeculae carneae. Adjacent to the interventricular septum the superior right ventricular wall is almost completely replaced by fat

The typical microscopic picture of myocardial fat infiltration is illustrated in Fig 2 Individual muscle fibers are separated

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Fig. 1. Drawing from gross specimen of myocardial fat infiltration. The alternating streaks in the right ventricle and septum are distinctly yellow in the original heart.

by sheets and cords of well-differentiated fat cells. An additional striking finding is the concomitant presence of myocardial fibrosis (Fig. 3). This is particularly true when significant amounts of fat are found in a subendocardial location. The rare case is characterized by substitution of more than 40 per cent of the myocardium by fat cells intermingled with bands of fibrous connective tissue (Fig. 4). In the latter situation the ventricular wall has a grossly discernible streaky pattern of alternating yellow-gray and red-brown.

Clinical correlations

A statistical comparison (t tests) of the fat infiltration group with a control group of equal mean age is summarized in Table I. The control group is typical of most series of autopsies in that it contains a preponderance of males. The fat infiltration group shows a significant reversal of this trend. In addition, in the fat-infiltration group there is a greater incidence of myocardial fibrosis and of postinfarction myocardial rupture. Differences in the incidence of coronary artery disease, myocardial infarction, congestive heart failure, sudden unexplained death, and hypertension could not be detected in the two groups.

Since myocardial fat infiltration is more common in women, all subsequent statistical comparisons are limited to the female sex.

The analyses summarized in Table II were designed to detect changes due to the general aging process. There are no significant differences in heart weight, ventricular thickness, or valve circumference between the sixth and eighth decades in this small series. However, a comparison of the fat infiltration group with a control group (Table III) reveals that in the former there is a significantly greater mean heart weight, which is also reflected in the thickness of the ventricular walls. The characteristics of general aging and fat infiltration are therefore different in terms of these parameters.

Table IV reveals the effects of myocardial fibrosis per se. In comparison to fat infiltration, myocardial fibrosis is associated with an even greater degree of hypertrophy. As indicated in Table I, myocardial fat infiltration is frequently associated with myocardial fibrosis. A division of the total fat infiltration group into those with fat alone (*Group A*, Table V) and those with fat plus fibrosis (*Group C*, Table V) reveals the relative significance of each factor. Myocardial fat infiltration per se is not associated with any statistically significant difference in the param-

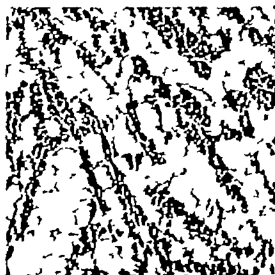


Fig. 2. Myocardial fat infiltration of the right ventricle. There is no evidence of myocardial fibrosis. (Hematoxylin and eosin, ×121.)

eters measured However the presence of concomitant myocardial fibrosis is associated with myocardial hypertrophy and this hypertrophy is probably first manifested by an increase in the thickness of the left ventricle.

These data may indicate that there are in fact two types of myocardial fat infiltration. A study of the microscopic sections prior to these quantitative comparisons led to a similar interpretation on a purely subjective basis.

In the first type of myocardial fat infiltration (Fig 2) fat cells are found most commonly in the right atrium and right ventricle. These cells occur in thin cords, and for the most part, both the cords and the cells composing them are relatively small There also appears to be a direct connection between the pericardial adipose tissue and the fat cells within the myocardium This type of fat infiltration is not associated with significant changes in heart weight or the circumference of individual valves.

The above-mentioned type of fat infiltration occurs alone in approximately half the cases. In the rest of the cases however fat infiltration is associated with significant areas of myocardial fibrosis which contain areas of fat metaplasia (Fig 3) This combination of findings indicates

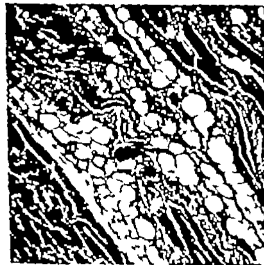


Fig 3 Myocardial fat metaplasia in an area of myocardial fibrosis. Note the hypertrophy of individual muscle fibers. (Hematoxylin and eosin ×127)



Fig 4 Myocardial fat replacing over 40 per cent of the thickness of the ventricular wall. (Hematoxylin and eosin ×32.)

degenerative myocardial disease and is associated with myocardial hypertrophy Of further interest is the fact that all three examples of cardiac rupture occurred in patients with both myocardial fat infiltration and myocardial fibrosis.

In terms of valve circumference the data do not appear to be statistically different in those areas designed to test the effects of aging and myocardial fat infiltration per se. Myocardial fibrosis is associated with significant valvular dilatation in a poorly predictable pattern in keeping with the random nature of the cicatrizing process. With fibrosis alone the mitral ring appears dilated (Table IV) whereas with fibrosis plus fat infiltration changes in the pulmonic and aortic rings (Table V) appear to predominate. We have no satisfactory explanation for these findings.

Discussion

The literature on myocardial fat infiltration is understandably brief We were unable to find a single reference during th past 10 years; the last comprehensive re-

Table I

	Control	*Myocardial fat infiltration*	*p*
Mean age	61	61	
Sex			0.05–0.01
Male	31	17	
Female	21	35	
Coronary artery			
Sclerosis	28	31	0.4–0.3
Occlusion	4	2	0.3–0.2
Myocardial			
Fibrosis	10	25	0.01
Infarct	7	5	0.4–0.3
Rupture	0	3	0.05–0.01
Congestive failure	9	6	0.3–0.2
Sudden death	3	4	0.4–0.3
Hypertension	6	7	0.4–0.3

view was published in 1933 by Saphir and Corrigan.[1] Although these authors failed to make note of the fact, their series likewise contained a preponderance of women (67 per cent). It was their opinion that myocardial fat infiltration is a plausible morphologic cause of otherwise unexplained sudden myocardial insufficiency and death. The present series contains no instance in which this statement can be supported. Our data do support the contention of Krumbhaar and Crowell[3] that cardiac rupture may occur in cases of myocardial fat infiltration only when there is concomitant evidence of previous coronary artery insufficiency. It has also been observed that cardiac rupture is more common in the aged female patient and occurs as a complication of myocardial infarction.[3] Schluter[4] was of the opinion that fat infiltration in areas of myocardial fibrosis was the result and not the cause of gradually occurring insufficiency of the myocardium.

The term "fat infiltration" is of course a poor one, especially since it connotes "invasion" of the myocardium by subepicardial adipose tissue. The fat probably arises through metaplasia of loose connective tissue. Fat infiltration occurs secondary to other processes in other sites of the body, but few investigators consider it an active process that causes pressure atrophy of the involved parenchyma. Unfortunately, the word "metaplasia" is poorly understood and infrequently used apart from histopathologic descriptions. Therefore, "myocardial fat infiltration" will probably continue to be the term by which this interesting finding is recorded.

Microscopic studies indicate that myocardial fat metaplasia occurs in two distinctly separate situations. The first of these (Fig. 2) is characterized by cords of fat cells intermingled with small atrophic muscle bundles. There is no accompanying myocardial fibrosis, and the fat cells often appear to be extending from the epicardium—hence the term "infiltration." In the second situation (Fig. 3) fat cells are surrounded by areas of productive fibrosis. Large areas of myocardium are replaced (Fig. 4); fat cells do not appear to be connected with the epicardial layer, and the whole process suggests active myocardial scarring as opposed to passive myocardial atrophy. The statistical re-

Table II. Control cases by decade (women only)

	Sixth decade N = 7	*6 vs. 7 (p)*	*Seventh decade N = 19*	*7 vs. 8 (p)*	*Eighth decade N = 15*
Heart weight (grams)	307	0.4–0.3	300	0.4–0.3	310
Right ventricular wall (cm.)	0.25	0.4–0.3	0.24	0.3–0.2	0.26
Left ventricular wall (cm.)	1.08	0.3–0.2	1.03	0.4–0.3	1.05
Valve circumferences (cm.)					
Tricuspid	11.18	> 0.4	11.19	> 0.4	11.19
Pulmonic	6.92	0.2–0.1	7.13	0.4–0.3	7.00
Mitral	8.96	0.3–0.2	8.79	0.2–0.1	9.05
Aortic	6.84	0.3–0.2	6.97	0.2–0.1	7.19

sults likewise support the contention that two processes are involved at least in terms of heart weight left ventricular thickness and the circumference of the aortic and pulmonic valves (Table V *A vs C*) In my opinion the former process ("infiltration") is analogous to disuse atrophy whereas concomitant fibrosis and fat metaplasia indicate active myocardial scarring secondary to coronary artery atherosclerosis and relative myocardial ischemia.

Table III

	Control cases (women only) N = 19	*Cases of fat infiltration (women only) N = 35*	*p*
Heart weight (grams)	300	364	< 0.005
Right ventricular wall (cm.)	0.24	0.29	0.05–0.025
Left ventricular wall (cm.)	1.03	1.18	0.025–0.01
Valve circumferences (cm.)			
Tricuspid	11.19	11.34	0.3–0.2
Pulmonic	7.13	7.18	> 0.4
Mitral	8.79	9.16	0.1–0.05
Aortic	6.97	7.09	0.3–0.2

Table IV

	Control cases (women only) N = 19	*Myocardial fibrosis (women only) N = 9*	*p*
Heart weight (grams)	300	419	<0.005
Right ventricular wall (cm.)	0.24	0.26	0.4–0.3
Left ventricular wall (cm.)	1.03	1.31	<0.005
Valve circumferences (cm.)			
Tricuspid	11.19	11.97	0.2–0.1
Pulmonic	7.13	7.58	0.1–0.05
Mitral	8.79	9.30	0.05–0.025
Aortic	6.97	7.13	0.3–0.2

Table V

	Group A		*Group B*		*Group C*	
	Fat infiltration alone (N = 16)	*A vs B (p)*	*Control group (N = 19)*	*B vs. C (p)*	*Fat infiltration with myocardial fibrosis (N = 19)*	*A vs. C (p)*
Heart weight (grams)	323	0.2–0.1	300	< 0.005	398	< 0.005
Right ventricular wall (cm.)	0.27	0.1–0.05	0.24	0.05–0.025	0.31	0.2–0.1
Left ventricular wall (cm.)	1.09	0.2–0.1	1.03	< 0.005	1.25	0.05–0.025
Valve circumferences (cm.)						
Tricuspid	11.50	0.2–0.1	11.19	> 0.4	11.21	0.2–0.1
Pulmonic	6.86	0.2–0.1	7.13	0.2–0.1	7.45	0.025–0.01
Mitral	9.22	0.1–0.05	8.79	0.2–0.1	9.11	0.4–0.3
Aortic	6.80	0.3–0.2	6.97	0.05–0.025	7.34	0.025–0.01

The data suggest that the occurrence of myocardial hypertrophy is manifest first in the right ventricle (Table V *A vs B*) in uncomplicated myocardial fat infiltration. At first glance this confirms the generally held impression that myocardial fat infiltration is more common and more extensive in the right ventricle. However this finding may also be an expression of inaccurate mensuration since the right ventricular thickness is logically determined with less precision when the epicardial fat blends imperceptibly with the adjacent muscle. Nevertheless the data hold true by indicating a predominance of left ventricular hypertrophy in cases of myocardial fibrosis (Table IV). The latter term is used here to indicate those hearts with myocardial evidence of long-standing coronary artery insufficiency. The interpretation of myocardial hypertrophy is at best difficult since left ventricular strain is a common cause of right ventricular hypertrophy.[5]

Summary

Myocardial fat metaplasia occurs with greatest frequency in women in the seventh decade. In approximately half the cases here is concomitant myocardial fibrosis and an increased incidence of postinfarction myocardial rupture, myocardial hypertrophy and increased thickness of the ventricular walls. These changes are not due to the general aging process or to fat infiltration per se.

Uncomplicated fat metaplasia has a histologic appearance distinct from that seen with associated myocardial fibrosis. The cardiac parameters herein studied were not significantly different from those of a control population of the same sex and age distribution. The two types of myocardial fat metaplasia are thus different on both morphologic and quantitative comparison.

REFERENCES

1. Saphir, O., and Corrigan, M.: Fatty infiltration of the myocardium, Arch. Int. Med. 52:410, 1933.
2. Krumbhaar, E. B., and Crowell, C.: Spontaneous rupture of the heart, Am. J. M. Sc. 170:828, 1925.
3. Zeman, F. D., and Rodstein, M.: Cardiac rupture complicating myocardial infarction in the aged, A.M.A. Arch. Int. Med. 105:431, 1960.
4. Schluter, P. R.: Die Erfahrung des hypertrophierten Herzmuskels, Vienna, 1906, Franz Deuticke. Cited by Saphir and Corrigan.[1]
5. Thompson, W. P., and White, P. D.: The commonest course of hypertrophy of the right ventricle—left ventricular strain and failure, Am. Heart J. 12:641, 1936.

The clinical significance of P waves with delayed ascent

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Differences in the contour of P waves as observed in the standard leads suggested the idea of exploring the clinical significance of these varieties. The well known electrocardiographic patterns of P pulmonale, mitrale, congenitale and cardiale, etc., although not characteristic of any particular lesion, are most often found in specific conditions. Studying the morphology of the atrial wave in cardiac patients, we often observed (in Standard Lead II) P waves with markedly delayed ascent which were easily recognizable by simple inspection and expressed exactly through the magnitude of their component angles (see Fig. 1). In addition, determination of the intersection of the height of the atrial triangle and its base line graphically expresses the degree of symmetry of the P wave. It was found that P waves with delayed ascent frequently appear in the electrocardiograms of patients with coronary heart disease, especially when this condition is accompanied by the clinical syndrome of angina pectoris. A systematic study was made with a view to establishing the morphologic particularities of this peculiar P wave and to correlating it with other electrocardiographic features and with the corresponding clinical picture.

Methods and material

Electrocardiograms recorded with a Sanborn apparatus while the subject was in the recumbent position were used in the present study. Because the delayed ascent was more evident in Lead II, the P wave was analyzed exclusively in this lead. In addition to the conventional description of this wave (such as height, shape and duration), the magnitude of each of its three angles and the rising—and falling—time of its ascending and descending limbs were determined according to methods previously described by the author.[1] The P-R interval, P-R segment, auricular T wave and Macruz index were determined in every case. Electrocardiograms were examined minutely and classified as being either normal or abnormal. The size of the heart was estimated fluoroscopically and classified as being either normal or slightly (+), moderately (++), or considerably (+++) enlarged. The clinical diagnoses were established on the usual bases of history, signs, symptoms, and laboratory and instrument evidence.

One thousand nonselected records, which formed part of our electrocardiographic archives, were examined in the search for P waves with delayed ascent.

Results

Table I reproduces all the measured data of P waves with delayed ascent in Lead II.

Incidence. A P wave with delayed ascent was found in , instances (per cent of the records).

Shape of the P wave. Pointed P waves were observed in 41 cases (56 per cent) and rounded P waves in 34 cases (44 per cent).

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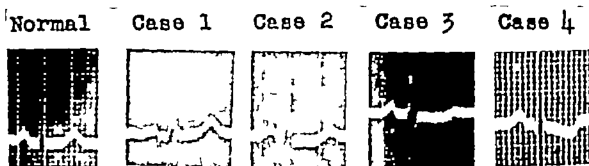


Fig 1 *Normal.* The P w[illegible] 1 4 [illegible] h[illegible] 0 09 sec in width Its ascending limb measures 0.015 sec., i.e. 30 per cent of P wave dur[illegible] ([illegible] [illegible]rdial infarction; the P wave is 0.8 mm. in height and 0 13 sec. in duration The as[illegible] 0 11 sec [illegible] e 84 per cent of the corresponding P-wave duration. *Case 2* Angina pector[illegible] the [illegible] 1 2 mm in h[illegible]ght and 0.12 sec. in duration. The ascending limb measures 0 09 sec i e 75 per [illegible] angina pector[illegible] the P wave is 1 4 mm. in height and 0.10 sec. in duration. The ascending [illegible] 0 08 [illegible] i e. 80 per cent of the duration of the P wave. *Case 4* Hyperten[illegible] [illegible] the P wave is 1 6 mm. in height, 0 11 sec in duration, and the ascending limb me[illegible] 0 09 [illegible] 82 p[illegible] of the duration of the corresponding P wave.

Duration of the P wave [illegible] duration measured [illegible] 0 10[illegible] [illegible] ±0 015 with ranges from 0 0[illegible] [illegible] 0 1[illegible] [illegible] Distribution of P wave [illegible] as follows 0 08 sec in 4 [illegible] ([illegible] per cent) 0 09 sec in 7 cases (9 1 per cent) 0 10 sec in 22 cases (28.6 per cent) 0 11 sec in 21 cases (27 2 per cent 0 12 sec in 12 cases (15 6 per cent) 0 13 sec in 7 cases (9 1 per cent) 0 14 sec in 2 cases (2 6 per cent) and finally 0 16 sec in 2 cases (2 6 per cent) If the upper limit of the normal P wave duration is considered to be 0 12 second this type of P wave had a normal duration in 66 cases (85 7 per cent) and a prolonged duration in 11 cases (14.3 per cent)

Quantitative aspects of the asymmetry of the P wave The average duration of the ascending limb of the P wave measured 0 08 sec ±0 012 i e 74 per cent of the duration of the P wave The descending limb lasted 0 029 sec. ±0 010 26 per cent of the P wave duration Accordingly the angle alpha or degree of elevation of the ascending limb from the base line was 32 0 degrees ±7 9 Angle beta or degree of descent from the base line averaged 57 6 degrees ±10 0 In consequence the average difference between the two basic angles of the atrial triangle reached 25 6 degrees.

Macruz index The average value of the Macruz index was 1 88 which indicated left atrial enlargement for the whole group Using the quantitative criteria of Macruz in evaluating the data of the present study we found that atrial cavities were of normal dimensions in 23 cases (29 8 per cent) and that right atrial enlargement existed in 14 cases (18 2 per cent) and left atrial enlargement in 40 cases (52 per cent)

Correlation with the electrocardiogram. The electrocardiogram was normal in 8 cases (10.3 per cent) whereas in 69 cases, i e in 89 7 per cent, it was definitely abnormal T_1 was positive in 25 cases (32.4 per cent) isoelectric in 13 cases (17 per cent) and negative in 39 cases (50.5 per cent) T_2 was positive in 41 cases (53.2 per cent) isoelectric in 15 cases (19 6 per cent) and negative in 21 cases (27.2 per cent).

Correlation with the radiologic heart size Normal heart size was found in 24 cases (31 2 per cent) A slightly enlarged heart was found in 39 cases (50 6 per cent) and a moderately enlarged heart in 14 cases (18 2 per cent)

Correlation with clinical diagnoses Coronary artery diseases (angina pectoris, myocardial infarction) were found in 69 cases (89 6 per cent) and congestive heart failure in 6 cases (7 8 per cent) whereas post infectious myocarditis and a normal heart were found in a single case each (1.3 and 1 3 per cent)

Discussion

The above-described variety of P wave with delayed ascent had the following characteristics its height measured on an

average 1.27 mm. ±0.37 which is entirely normal For the mean amplitude of the normal P wave in Lead II Ashman and Hull[2] indicate 1.25 mm Thomas and Dejong[3] 1.3 mm Lepeschkin[4] 1 4 mm Stewart and Manning[5] 1 4 mm. ±0.53 and Sano and associates[6] 1.3 to 1 4 mm. Its duration measured 0 109 second ±0 015 on an average. Our figure coincides almost exactly with that found by Caceres and Kelser[7] in a group of 50 healthy subjects mean duration of the normal P wave amounted to 0 108 second By general agreement the upper limit of the normal duration of the P wave is set at 0 11 to 0 12 second (Goldberger[8] Burch and Winsor[9] Graybiel and co-workers,[10] Bradley and Marriott[11]) Consequently the P wave with delayed ascent is of normal height and of normal duration in 85 7 per cent and of prolonged duration in 14.3 per cent.

The normal peaked P wave exhibits an almost symmetrical structure. In middle-aged subjects, the rising time, i.e duration of the ascending limb of the P wave occupies 49 4 per cent of the duration of the P wave. Since the average magnitudes of angles alpha and beta are 44 and 51.5 degrees, respectively the average difference reaches 6.5 degrees. In cases of P waves with delayed ascent the rising time occupies 74 per cent of the duration of this wave, i.e. deviated from the center by 24 per cent. Because angle alpha measures 32 degrees and angle beta 57 6 degrees, on an average the average difference between the two basal angles is 25 6 degrees.

A P wave with delayed ascent is a definitely abnormal electrocardiographic finding It was found overwhelmingly (89 6 per cent) in patients with coronary artery diseases either with angina pectoris or with myocardial infarction. In 7 8 per cent of the cases observed the patients had congestive heart failure and coronary artery disease could not be definitely excluded In only one case was the heart found to be normal. Its pathologic significance was demonstrated directly by the corresponding electrocardiogram—abnormal in 89 7 per cent—and by the fluoroscopically observed heart size which was increased in 68 8 per cent of the observations.

Impairment of the blood supply to the auricular muscle due to coronary arteriosclerosis may produce changes in the graphic aspect of the P wave Lengthening of the P wave duration over 0 12 second intra atrial block is a common manifestation of coronary sclerosis that Bradley and Marriott[11] observed in 203 instances, i.e. in 4.5 per cent of 4,500 records. Experimental occlusion of Condorelli s artery or clamping of Bachmann s bundle has been shown to produce intra-atrial block and even at times, atrial dissociation (Condorelli[12] Scherf and Siedeck[13]) Hundt and Schlemmer[14] observed progressive lengthening of P duration with advancing age, possibly correlated with increasing coronary arteriosclerosis. The author investigated the influence of age on the symmetry of the atrial wave in normal subjects[1] and found a definite correlation In young subjects (up to 20 years of age) the rising time averaged 45 7 per cent in those of middle age (from 21 to 50 years) it averaged 49 4 per cent and in aged subjects (over 51 years) the average duration of the ascending limb of the atrial triangle occupied on an average 60 9 per cent of the duration of the P wave Similarly the

Table I Measured magnitudes of P waves with delayed ascent

	Age (yr)	Rate (min)	Height (mm)	Duration (sec)	Rising time		Falling time		P R interval (sec)	P R segment (sec)	Macruz index	Angle (degree)		
					sec	%	sec	%				α	β	γ
Mean	56.1	78 9	1.27	0 109	0 08	74	0 029	26	0 178	0.069	1.88	32.0	57 6	90.4
S.D			0.37	0.015	0 012	8	0 010	8	0.023	0 022	0 66	7.9	10 0	14.1
Range	21	60	0 6	0.07	0.06	60	0	0	0 13	0 01	0 8	14 0	40 0	61.0
	76	106	2.2	0 16	0 12	100	0.06	43	0 24	0.12	13.0	47.0	90 0	127.0

angle of ascension alpha decreased with age. Its magnitude in the young-age group was 48 7 degrees, on an average in the middle-age group it averaged 45 degrees, and in the group of aged subjects it measured 41 9 degrees. Consequently a definite tendency exists for a physiologically delayed ascent of the P wave in healthy subjects as they advance in years. This may be explained by the increasing frequency of arteriosclerosis in the atrial wall. The frequent occurrence and more pronounced degrees of delayed ascent of the P wave, independent of age, in cases of coronary sclerosis may be explained by a lesion of the atrial myocardium caused by a deficient supply of blood.

The exact mechanism of production of P waves with delayed ascent is unknown. Scheuer and associates,[15] investigating the atrial vectorcardiogram in health and disease in patients with coronary artery disease observed P loops of abnormal duration orientation and configuration What particular modification of the P loop may be present in the frontal plane and with a favored projection on the axis of Lead II that is reflected in the form of a delayed ascent needs further explanation

Summary

1 P waves with delayed ascent were encountered with an incidence of 7 7 per cent among 1,000 nonselected records.

2 The ascending limb occupied 74 per cent (instead of the normal 49 4 per cent) and the angle alpha which measures the degree of elevation of the ascending limb amounted to 32 degrees (instead of the normal 44 degrees) Both values express the remarkable asymmetry of the P wave with delayed ascent.

3 P waves with delayed ascent are definitely abnormal waves. They were found to be associated with coronary artery disease in 89 6 per cent of the cases, and with heart failure in 7 8 per cent of the cases.

REFERENCES

1 Gross, D Contributions to the functional morphology of the P wave, Am. Heart J 61:436, 1961.

2. Ashman, R., and Hull, E. Essentials of electrocardiography New York, 1941, The Macmillan Company

3 Thomas P., and Dejong, D The P wave in the electrocardiogram in the diagnosis of heart disease, Brit. Heart J 16:241 1954.

4. Lepeschkin, E. Modern electrocardiography Baltimore, 1951 Williams & Wilkins Company p. 221

5. Stewart, C. B and Manning G. W A detailed analysis of the electrocardiogram of 500 R.C.A.F Aircrew Am. Heart J 27:502, 1944

6. Sano, T Hellerstein, H K., and Vayda, E. P vector loop in health and disease as studied by the technique of electrical dissection of the vectorcardiogram Am. Heart J 53:854, 1957

7 Caceres, C. A., and Kelser G. A. Duration of the normal P wave, Am. J Cardiol. 3:449 1959

8. Goldberger E. Unipolar lead electrocardiography and vectorcardiography Philadelphia, 1953 Lea & Febiger p. 137

9 Burch, G E. and Winsor T A primer of electrocardiography Philadelphia, 1955 Lea & Febiger p. 19

10 Graybiel, A., McFarland, R. A., Gates, D C. and Webster F A Analysis of the electrocardiograms obtained from 1 000 young healthy aviators, Am. Heart J 27:524, 1944

11 Bradley S. M and Marriott, H. J L. Intra atrial block, Circulation 14 1073 1956.

12. Condorelli, L. Experimentelle Untersuchungen über die interaurikuläre Reizleitung Ztschr ges. exper Med. 68:516, 1929

13 Scherf D and Siedek, H. Über Block zwischen beiden Vorhöfen, Ztschr klin. Med. 127:77 1934.

14. Hundt, H J and Schleimmer H. J Zur Häufigkeit der Verbreitung der Vorhofzacke im Elektrokardiogramm und mögliche Beziehungen zur Koronarsklerose, Ztschr Kreislauf forsch 48:1120, 1959

15. Scheuer J Kahn M Bleifer S., Donoso, E., and Grishman, A. The atrial vectorcardiogram in health and disease Am Heart J 60:33 1960.

The role of the dilated pulmonary artery in abnormal splitting of the second heart sound

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Splitting of the second heart sound is due to asynchronous closure of the aortic and pulmonary valves.[1] Almost a hundred years ago Potain[2] observed this phenomenon in health during normal respiration but it is only in recent years[3] that closure of the aortic valves has been shown to precede closure of the pulmonary valves.

Normally the right ventricle is distended by the systemic venous return. This is augmented during inspiration resulting in prolongation of right ventricular systole and delay in closure of the pulmonary valve; the pulmonary second sound (P_2) moves away from the first sound, thus widening the splitting of the second sound.[4] With expiration right ventricular filling is diminished and P_2 moves closer to the first sound. At the same time the augmented pulmonary venous return which has now reached the left ventricle, delays closure of the aortic valve so that the aortic second sound (A_2) moves away from the first sound[4,5] thus A_2 and P_2 become superimposed. During held expiration a relatively "steady state" develops with P_2 following A_2 after a fairly constant interval (usually less than 0.04 second).

In diseased states, abnormally wide splitting of the second sound which can be appreciated at the bedside, has usually been attributed to two causes. These are prolongation of right ventricular systole and delay in electrical activation of one ventricle or the other. The former occurs in systolic overload of the right ventricle (pulmonary stenosis[7-9]) diastolic overload of the right ventricle (atrial septal defect[10,11]) and most strikingly when the two are associated. The latter is encountered in ventricular aberration or bundle branch block,[3,12,13] ventricular premature systoles,[14] and paroxysmal ventricular tachycardia.[14]

Premature closure of the aortic valves due to shortening of left ventricular systole occurs in mitral incompetence[15,3] and produces abnormally wide splitting on the phonocardiogram. This is usually not appreciated at the bedside since A_2 is usually obscured by the systolic murmur. The wide splitting often encountered in ventricular septal defect without pulmonary hypertension or pulmonary stenosis[17] may be due to a similar mechanism.[4,18]

The purpose of this paper is to draw attention to the role of recoil of the pul

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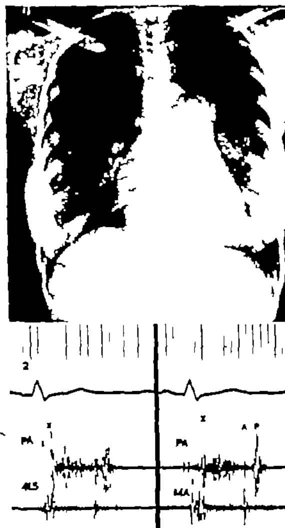


Fig 1 Patient 1 The skiagram shows the marked dilatation of the main pulmonary artery with normal peripheral arteries. A calcified tuberculous focus can be seen closely associated with the dilated artery The phonocardiogram shows the loud pulmonary ejection click maximal at the pulmonary area and the widely split second sound Note the broad I composed of several high-frequency vibrations.

monary artery a hitherto undescribed factor in determining the time of closure of the pulmonary valve

Material and methods

From a large series of patients studied clinically and phonocardiographically nine were selected for analysis because of abnormally wide splitting of the second sound unassociated with pulmonary stenosis left to-right shunt or delayed electrical activation of the ventricles. Full clinical examination with special attention to auscultation was carried out in every case particular attention was paid to the presence of a pulmonary ejection click[10] a pulmonary flow murmur the degree of splitting and the effect of respiration

High frequency (logarithmic) sound tracings were recorded on a 6-channel* recording apparatus with two phonocardiographic channels as described elsewhere.[9] Sound tracings were recorded synchron ously with electrocardiograms and usually

*New Electronic Products, London, England

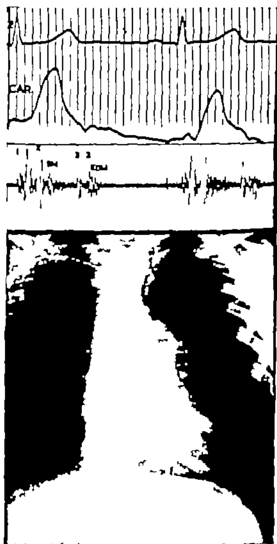


Fig 2 Patient 5 The phonocardiogram shows splitting of the first sound and a widely separated loud pulmonary ejection click. I is widely separated from A_2 and a short pulmonary diastolic murmur is present The x-ray film shows the marked dilatation of the main pulmonary artery with normal peripheral pulmonary vessels.



Fig. 3 Patient 7 The x-ray film shows the enlarged main pulmonary artery and normal peripheral arteries. The phonocardiogram show wide splitting of the first sound and a late pulmonary ejection click. Wide splitting of the second heart sound is present

with indirect carotid jugular right ventricular or pulmonary arterial tracings on separate occasions. The components of the heart sounds were identified by methods previously described.[11] The phonocardiograms were always taken during held expiration at fast paper speed (75 to 80 mm per second). The effects of respiration on the degree of splitting were not studied in every subject

All measurements were made in at least 5 cycles in held expiration. The maximum degree of splitting during normal inspiration was recorded in 5 patients. The time interval between the beginning of the first sound and the beginning of the pulmonary ejection click and the interval between the beginning of A_2 and P_2 were measured

All the patients were catheterized. Intracardiac shunts were excluded in the first 5 by gas analysis only but in the latter 4

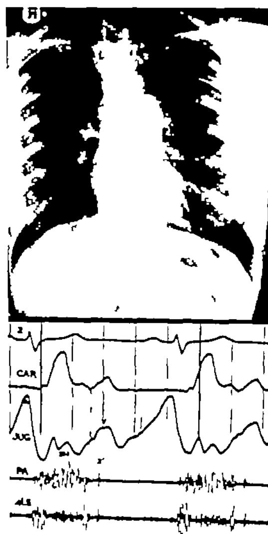


Fig. 4 Disproportionate splitting of the second sound is present in a patient with mild pulmonary stenosis (RVP 42/4; PAP 16/10)—0.08 sec. on expiration and 0.1 sec. on inspiration, associated with marked poststenotic dilatation of the main pulmonary artery

Table I

Patient	*Age (yr.)*	*Sex*	*Condition*	*R.V.P. (mm.Hg)*	*P.A.P. (mm. Hg)*
1. R.A.	13	M	Idiopathic dilatation of pulmonary artery	14/0	14/9
2. M.J.	21	F	Idiopathic dilatation of pulmonary artery	Normal	No gradient
3. C.S.	23	M	Idiopathic dilatation of pulmonary artery	30/4	29/10
4. H.B.	30	F	Idiopathic dilatation of pulmonary artery + pulmonary incompetence	28/0	22/7
5. I.R.	7	M	Idiopathic dilatation of pulmonary artery + pulmonary incompetence	30/0	24/14
6. H.V.	34	F	Idiopathic dilatation of pulmonary artery + pulmonary incompetence	20/0	14/5
7. R.E.	16	F	Atrial septal defect postop.	28/4	15/7
8. F.R.	20	F	Atrial septal defect postop.	22/0	13/4
9. J.S.	22	F	Atrial septal defect postop.	—	—

oximetry and dye-dilution methods were also employed.

Results

The results are shown in Table I. An abnormally wide degree of splitting of the second sound was found in all subjects (Figs. 1 to 3); the splitting widened in the normal fashion on inspiration and P_2 moved farther away from A_2. P_2 was sometimes unusually broad and loud. It consisted of several equal vibrations and extended over periods up to 0.04 second (Fig. 1).

The electrocardiogram was completely normal in 5 patients. The 3 patients with repaired atrial septal defects still showed slurred complexes in Lead V_1 but the QRS complexes were narrow. The right ventricular and pulmonary arterial pressures were normal in all patients. Withdrawal tracings across the pulmonary valve showed no gradient in 3 patients or only a trivial gradient at valve level (Table I).

All the patients had markedly enlarged sometimes aneurysmal main pulmonary arteries (Figs. 1 to 3) but the right and left pulmonary arteries as seen on the x-ray film did not appear to be affected. During catheterization in several patients the catheter could be coiled in the main artery to form a large loop which outlined the greatly dilated chamber.

Patients 1 to 3 appeared to have no abnormality apart from the pulmonary arterial enlargement and were regarded as suffering from idiopathic dilatation of the pulmonary artery.[illegible] One of these (Patient 1) had tuberculosis of the left upper lobe with a calcified focus (Fig. 1) so that adhesions between the lung and the main pulmonary artery may well have played a part in the arterial dilatation or even healed tuberculous arteritis may have been present. There was no real change in physical signs or radiologic appearances over a 5-year period of observation. In Patients 4 to 6 slight pulmonary incompetence was diagnosed in view of a Grade 1 to 2/4 short early diastolic murmur in the pulmonary area (Fig. 2). The incompetence was assessed as trivial in view of the softness and shortness of the murmur, the normal pulmonary arterial diastolic pressures, the normal size of the heart radiographically and radioscopically, and the normal electrocardiograms. In Patient 6 the two-venous-catheter technique[illegible] failed to show any regurgitant dye. These subjects were thought to be suffering from "idiopathic pulmonary artery dilatation" with slight pulmonary incompetence due to dilatation of the annulus. Three patients with signs and catheter findings suggestive of significant degrees of idiopathic pulmonary incompetence associated

Splitting of second heart sound		S_1-click (sec.)	QRS (sec.)	Axis (degrees)	Lead 1	Cardio-thoracic ratio	Comment
Expiration (sec.)	*Inspiration* (sec.)						
0 06	0 10	0 06	0 09	+105	rR/S	50	
0 05	0 07	0 04	0 08	+105	r/S	46	
0 06	0 10	0 06	0 06	+70	/S	44	Patent ductus arteriosus postop.
0 05	—	—	0 10	+30	r/S	45	
0 09	—	0 10	0 08	+70	/S	42	Split S_1 of 0.04 sec.
0 04	—	0 03	0 07	+110	/S	40	
0 07	0 09	0 05	0 07	+85	rr/S	41	Split S_1 of 0 04 sec
0 06	0 10	0 08	0 08	+105	qR	<50	
0 06	—	0 06	0 06	+80	rsr	41	No murmur

with dilatation of the pulmonary arteries were excluded although the degree of splitting in these cases was no greater

Three patients (Patients 7 8 and 9) were investigated 1 year after surgical closure of secundum atrial septal defects. Two were studied by cardiac catheterization and dye-dilution methods which showed complete repair of the defect. Only a trivial gradient at valve level remained with normal right ventricular pressures. The third had a trivial gradient across the pulmonary valve of 7 mm. Hg with a normal right ventricular pressure prior to operation. Since all murmurs disappeared she was studied by dye-dilution methods only which showed complete repair of the defect. All 3 patients showed persistence of pulmonary arterial dilatation (Fig 3)

Discussion

We have studied a series of 9 patients in whom exceptionally wide splitting of the second sound was present during expiration and in whom the usual causes of abnormal splitting could not be found. Thus, there was no evidence of any condition such as significant pulmonary stenosis* or atrial septal defect which is known to prolong right ventricular systole nor was there any evidence of delayed electrical activation of the ventricles. There was also no evidence of any condition associated with early closure of the aortic valve. Some other cause for delayed closure of the pulmonary valve had to be implicated.

The feature common to all these patients was the marked enlargement of the main pulmonary artery In several patients this was amply confirmed by coiling a catheter in this dilated chamber It seems probable therefore that the abnormally dilated pulmonary artery was related to the abnormally wide splitting At the same time it is clearly recognized that abnormally wide splitting does not always occur when the pulmonary artery is markedly dilated since many of our patients with pulmonary arterial dilatation did not have abnormally split second sounds. Since the condition was benign in every patient, no pathologic study of the pulmonary arteries was available. However it is postulated that in some patients particularly those with "idiopathic pulmonary artery dilatation

For footnote see opposite column.

*Although 5 of the 8 patients catheterized showed trivial gradients across the pulmonary valve, the fact that all had normal right ventricular pressures and very large main pulmonary arteries favors idiopathic dilatation of the pulmonary artery[10,11] and not mild stenosis of the pulmonary valve with disproportionate poststenotic dilatation. Even if it is argued that these patients have mild pulmonary stenosis, it must be accepted that a trivial degree of stenosis of this order would not prolong right ventricular systole sufficiently to account for the marked delay in closure of the pulmonary valve.

Experimental and laboratory reports

The vectorcardiographic findings in left bundle branch block

A study using the Frank lead system

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The purpose of this paper is to present the vectorcardiographic findings in 14 adult patients with left bundle branch block. Previous reports have generally agreed on the gross characteristics of the orcardiogram in left bundle branch 'ock. Considerable controversy exists however in regard to the direction magnitude and origin of the earliest forces of the QRS complex.

In this laboratory we have used the corrected lead system proposed by Frank,[1] which possesses the advantage of approximately true orthogonality. In addition we have utilized the advantage of time expansion (achieved by recording data on magnetic tape and later reproducing it at a slower speed) to visualize the initial and terminal events of the QRS loop with clarity.[2] It is our opinion that recordings made with such techniques result in a more accurate presentation of the electrical activity of the heart than could previously be attained. Furthermore we feel that the quantitative characteristics of vectorcardiograms obtained by such techniques can be discussed in relation to experimental data concerning ventricular depolarization.

Methods

The Frank lead system was used in this study with 50,000 ohms as the unit of resistance. The chest electrodes were placed at the level of the fifth intercostal space and patients were studied in the supine position. The three scalar components were amplified by Sanborn 350-3,200 preamplifiers and recorded on an Ampex FR 100A tape recorder-reproducer. The appropriate voltages were selected from the tape and displayed on a Tektronix Type 502 dual-beam oscilloscope as the frontal horizontal and right sagittal projections of the spatial vectorcardiogram. Loops were photographed with a Hewlett Packard oscilloscope camera. A complete description of our vectorcardiographic recording system is presented elsewhere.[2]

Details of our method of loop analysis are presented in a separate publication.[3] Briefly we identified the Q R and S loops and measured the magnitude, angular direction and time of occurrence of each vector. The length and width of the loops were measured and a length-to-width ratio was calculated. The spatial magnitudes of the Q R and S vectors were calculated

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from their projections on the X Y and Z axes.

Fourteen adult male patients constituted the study group. The ages of the patients ranged from 26 to 70 years, with a mean of 58 years. Each patient in this study had complete left bundle branch block by standard electrocardiogram. The clinical features of each patient are indicated in Table I

Results

A Frontal plane (*Table II*) In the frontal plane a Q loop could be defined in only 3 of the 14 patients. In the other 11 the tracing started directly to the left, and usually inferiorly with no major change of direction within the first 20 milliseconds. R loops could be identified in all 14 patients, and were directed to the left and inferiorly in 11 to the left and superiorly in 3 An S loop could be identified in only 2 patients. The afferent limb of the QRS loop was displaced superiorly and was straight in the other 12 patients. J" displacement was evident in 8 of the 14 patients. Ten of the loops were counterclockwise in the frontal plane, 2 were clockwise, and 2 were figure of eight.

B Horizontal plane (*Table III*) Q loops in the horizontal plane could be defined in all patients. The Q vector was directed to the left in 13 At the apex of the Q loop the tracing usually changed direction abruptly and moved posteriorly until it reached the R point. The afferent limb of the loop was straight in the majority of patients. An S loop could be identified in only 2 J displacement was evident in 12 patients. Six patients had clockwise loops 7 had figure-of-eight loops, and one had a counterclockwise loop.

C Sagittal plane (*Table IV*) Q loops in the sagittal plane could be identified in all patients. The Q vector was always directed anteriorly and usually inferiorly After the Q loop the tracing moved posteriorly and inferiorly until it reached the R point. S loops could be identified in only 2 of the patients. The afferent limb of the loop was straight in the other 12 J displacement was evident in 11 patients. In this plane, 9 patients had clockwise loops, 4 had figure-of-eight loops and one had a counter clockwise loop.

The mean values for the magnitudes of the spatial Q and R vectors are presented in Table V

The initial forces of the loop in each of the three planes are presented in Fig 1 A typical tracing recorded from a patient with left bundle branch block is presented in Fig 2

Discussion

A statistical comparison of loops recorded from these 14 patients with those from 100 normal control subjects was

Table I *Clinical data*

Case number	Age (yr.)	Blood pressure (mm. Hg)	Myocardial infarction	Angina	LVH*	Digitalis
1	65	160/100	−	−	+	+
2.	26	120/75	−	+	−	−
3	66	200/110	−	?	+	−
4.	67	100/85	−	−	+	+
5	70	170/80	?	+	−	+
6.	64	80/60	+	+	+	+
7	61	120/75	+	+	+	+
8.	68	155 94	−	−	−	−
9	68	135/85	−	−	−	+
10	68	160/85	+	−	−	−
11	46	120/70	−	−	−	−
12.	56	120/80	−	+	−	−
13.	40	100/60	−	−	+	+
14.	40	130/90	+	+	−	−

*Those with clinical evidence of left ventricular hypertrophy

Table II. Frontal plane data

	Q angle (degrees)	Q magnitude (mv.)	Q time (msec.)	R angle (degrees)	R magnitude (mv.)	R time (msec.)	Loop length (mv.)	Loop width (mv.)	L/W ratio	QRS duration (msec.)
Normal										
Mean	−150	10	8	+36	1.25	35	1.39	0.29	5.97	76
S.D.	±56	±0.06	±3	±13	±0.33	±6	±0.35	±0.15	±3.63	±10
LBBB										
Mean	—	—	—	+22	1.05	55	1.22	0.60	2.13	131
S.D.		—	—	±26	±0.38	±15	±0.44	±0.22	±0.73	±21
Difference means	—	—	—	14	0.20	20	0.17	0.31	3.84	55
p Value	—	—	—	<0.005	<0.05	<0.001	<0.20	<0.001	<0.001	<0.001

Presented are the mean and one standard deviation for 100 normal subjects as well as the 14 patients with left bundle branch block (LBBB). The p values for the differences are also noted.

carried out. The data concerning this comparison are presented in Tables II, III, and IV for each plane. The magnitudes of the spatial vectors are compared in Table V.

In the frontal plane the Q loop was usually absent in patients with left bundle branch block. The R vector was displaced to the left and delayed in inscription. The magnitude of the R vector was greater than normal. There was no significant difference in the length of the loop. The width of the loop, however, was greater in those with left bundle branch block.

In the horizontal plane the Q loop was inscribed anteriorly in all patients, and to the left in all but one. In patients with normal ventricular conduction the Q loop is usually inscribed to the right and anteriorly. There was no significant difference between the two groups with respect to the magnitude of the Q vector. The R vector was displaced posteriorly and delayed in inscription in the patients with left bundle branch block. The R vector was also of greater than normal magnitude. The length of the loop and the length-to-width ratio were both significantly greater in those with left bundle branch block.

In the sagittal plane the Q vector was directed anteriorly and inferiorly in all but one case. In most normal subjects the Q vector is directed anteriorly and superiorly. There was no significant difference between the two groups with respect to the magnitude of the Q vector. An earlier time of occurrence of the Q vector was noted in patients with left bundle branch block in this plane only. This difference, although statistically significant, was probably an artifact related to the difficulty in measurement of the duration of forces directed to the left and therefore perpendicular to this plane. The R vector was displaced posteriorly and delayed in its time of inscription. The magnitude of the R vector was significantly greater than normal. The length of the loop and the length-to-width ratio were significantly greater in those with bundle branch block.

A comparison of the spatial magnitudes of the Q and R vectors revealed that the Q vector was of normal magnitude and the R vector was of greater than normal magnitude. A comparison of the spatial orientation of these vectors revealed that the Q vector was displaced to the left and inferiorly and that the R vector was displaced posteriorly and superiorly in relation to their positions in normal subjects. QRS duration was significantly greater than normal in all planes.

In patients with left bundle branch block a separate analysis of the afferent and efferent limbs of the QRS loop revealed significant delay of both. The time from the onset of the QRS complex to the R point (efferent limb) had a mean delay of 18 msec. The time from the R point to the

end of the QRS complex (afferent limb) had a mean delay of 42 msec.

An understanding of the genesis of the QRS complex in left bundle branch block in human beings necessitates a knowledge of the pathways of ventricular depolarization in this abnormal state. The majority of studies pertaining to this problem have been carried out in dogs. Preliminary observations support the view that the electrical events associated with cardiac depolarization are strikingly similar in the two species.

We have chosen to accept the data presented by Becker, Scher, and Erickson[4] in regard to ventricular depolarization in experimental left bundle branch block. The following discussion is an attempt to correlate our vectorcardiographic findings with the data presented by these authors. In addition, certain features of the intracavitary tracings in left bundle branch block will be discussed.

It is clear from our studies of the Q loop that the initial forces of ventricular depolarization are directed anteriorly, to the left, and usually inferiorly in the presence of left bundle branch block. Frimpter and co-workers[3] also noted in a vectorcardiographic study that the majority of patients with complete left bundle branch block had anterior initial forces. Becker and associates

Table III. Horizontal plane data

	Q angle (degrees)	*Q magnitude (mv.)*	*Q time (msec.)*	*R angle (degrees)*	*R magnitude (mv.)*	*R time (msec.)*	*Loop length (mv.)*	*Loop width (mv.)*	*L/W ratio*	*QRS duration (msec.)*
Normal										
Mean	+114	0.16	10	+1	1.05	37	1.18	0.67	2.05	82
S.D.	±25	±0.09	±4	±18	±0.32	±3	±0.35	±0.29	±1.10	±8
LBBB										
Mean	+71	0.14	8	−70	.06	55	2.33	0.59	4.51	143
S.D.	±21	±0.08	±3	±15	±0.43	±9	±0.63	±0.20	±2.13	±21
Difference means	43	0.02	2	71	1.03	18	1.15	0.08	2.46	61
p Value	<0.001	<0.40	<0.05	<0.001	<0.001	<0.001	<0.001	<0.40	<0.001	<0.001

Table IV. Right sagittal plane data

	Q angle (degrees)	*Q magnitude (mv.)*	*Q time (msec.)*	*R angle (degrees)*	*R magnitude (mv.)*	*R time (msec.)*	*Loop length (mv.)*	*Loop width (mv.)*	*L/W ratio*	*QRS duration (msec.)*
Normal										
Mean	−19	0.13	11	+96	0.81	37	0.96	0.61	1.79	83
S.D.	±33	±0.08	±4	±23	±0.33	±4	±0.35	±0.26	±0.94	±17
LBBB										
Mean	+16	0.13	8	+169	1.91	54	2.02	0.71	4.46	149
S.D.	±30	±0.06	±3	±10	±0.44	±8	±0.64	±0.59	±2.50	±46
Difference means	35	0.03	3	73	1.10	1	1.06	0.10	2.67	66
p Value	<0.001	<0.50	<0.001	<0.001	<0.001	<0.001	<0.001	<0.10	<0.001	<0.001

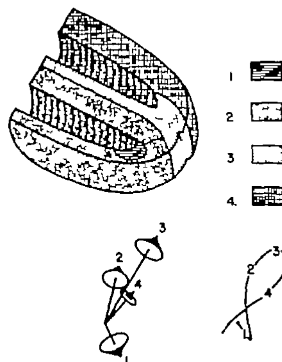


Fig 3 Genesis of the QRS complex. The figure illustrates four stages in the activation of the heart in left bundle branch block. The heart is viewed from the frontal plane. *Vector 1* Activation in the anterior paraseptal region of the right ventricle. *Vector 2* The dominant septal forces. *Vector 3* Terminal septal forces and early forces in the paraseptal region of the left ventricle *Vector 4* Activation of the lateral and superior aspects of the left ventricular free wall A horizontal plane view of the vectors and their resultant QRS_H loop is shown.

than in the earlier portions of this limb. We have wondered whether the more normal endocardial to epicardial spread during the latest stages of left ventricular free wall depolarization might not account for this.

It is clear from our studies that the major factor contributing to the prolongation of the QRS complex in left bundle branch block occurs in the initial half of the afferent limb of the loop. Becker and associates have suggested that the delay during the comparable period in the dog is attributable to the abnormal pathways of depolarization in the left ventricular free wall

From the previous discussion we would suggest that the vectorcardiogram in left bundle branch block may be reconstructed on the basis of four main vectors (see Fig 3) The first vector represents initial anterior forces recorded from the anterior paraseptal portion of the right ventricle The second vector results predominantly from right to-left activation of the interventricular septum The third vector represents the resultant of the terminal forces within the septum plus epicardial to endocardial spread at the septal borders of the left ventricular free wall The fourth vector represents depolarization as it courses from endocardium to epicardium in the lateral portions of the left ventricular free wall

Summary

In this report the characteristics of the vectorcardiograms recorded from 14 patients with left bundle branch block are presented We have used the corrected lead system proposed by Frank which possesses the advantage of true orthogonality We have recorded the scalar components of the vectorcardiogram on magnetic tape and reproduced the loop at a slow speed on the face of an oscilloscope The use of an orthogonal lead system allows one to interpret with quantitative accuracy the spatial characteristics of the vectorcardiogram The use of magnetic tape with its advantage of time expansion avoids the problem of center flare and leads to increased clarity of the initial and terminal events of the loop.

The results of our study are presented in tabular form and compared statistically with the findings in 100 normal control subjects. The characteristics of the spatial vectorcardiogram in left bundle branch block are discussed and a description of the genesis of the QRS complex is presented in relation to experimental data concerning the pathways of ventricular activation in this abnormal condition.

REFERENCES

1 Frank, E. An accurate clinically practical system for spatial vectorcardiography Circulation 13:737 1956.
2. Estes, E. H Jr., McCall, B., and Wallace A. G : Time expansion in vectorcardiography the advantages of magnetic tape recording Am. Heart J 63:95, 1962.
3 McCall, B Wallace, A. G and Estes, E. H Jr The characteristics of the normal vectorcardiogram a study using the Frank lead system Am. J Cardiol (in press).
4 Becker R. A Scher A. M., and Erickson, R. V Ventricular excitation in experimental left bundle branch block, Am. Heart J 55:547 1958.

5. Frimpter, G. W., Scherr, L., and Ogden, D.: The spatial vectorcardiogram in complete left bundle branch block, with special reference to the initial component, Am. Heart J. 55:220, 1958.
6. Sodi-Pallares, D.: New bases of electrocardiography, St. Louis, 1956, The C. V. Mosby Company, p. 279.
7. Sodi-Pallares, D., and Rodriguez, M. I.: Morphology of the unipolar leads recorded at the septal surfaces: its application to the diagnosis of left bundle branch block complicated by myocardial infarctions, Am. Heart J. 43:27, 1952.
8. Wener, J., Scherlis, L., and Sandberg, A. A.: The spread of the excitatory process and the left ventricular cavity potentials in left bundle branch block as studied with esophageal leads, Am. Heart J. 41:864, 1951.
9. Rodriguez, M. I., and Sodi-Pallares, D.: The mechanism of complete and incomplete bundle branch block, Am. Heart J. 44:715, 1952.

The vectorcardiographic QRSsE-loop findings in inferoposterior myocardial infarction

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The purpose of this report is to describe the QRSsE loop abnormalities observed in vectorcardiograms recorded with the Frank lead system in 153 cases of inferoposterior myocardial infarction. The terminology used in this paper to designate various types of infarction is based upon the effective electrical location of the infarction.[1-4] For example, an inferoposterior myocardial infarction is one whose effective electrical location is in the inferoposterior portion of the left ventricular wall. Since the infarcted myocardium is rendered electrically inert, the depolarization forces normally contributed by this region to the balance of forces which determine the mean instantaneous QRS spatial vectors are, in effect, subtracted from the electrical field of the heart (Fig. 1). It is much as though the infarction has given rise to new abnormal forces which are directed away from the electrical site of the infarction and which produce the characteristic QRS abnormalities of infarction in the appropriate leads of the electrocardiogram. It is evident that a method of terminology such as this, based as it is upon changes in the balance of electrical forces produced by the heart, makes it possible to avoid for the most part the not infrequent discrepancies which have been noted in the past between the anatomic location and the electrical manifestations of a given type of myocardial infarction.

In accordance with the terminology just described, it is possible to distinguish the following types of inferoposterior myocardial infarction: (1) diaphragmatic (inferior) infarction, (2) posterolateral myocardial infarction, (3) diaphragmatic-posterolateral myocardial infarction, and (4) strictly posterior myocardial infarction.

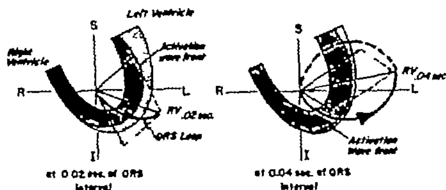
Material and methods

The cases selected to be included in this study series had to satisfy the following requirements: (1) There had to be clinical data indicative of arteriosclerotic and atherosclerotic heart disease with recent or past myocardial infarction, and (2) the conventional QRS criteria for the electrocardiographic diagnosis of recent or healed inferoposterior myocardial infarction had to be satisfied in each instance. These criteria are listed below.

A. Diaphragmatic infarction: a Q wave in Lead III of 0.04-second duration with a depth exceeding 25 per cent of the amplitude of the following R wave, if present

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A. NORMAL



B. AFTER DIAPHRAGMATIC INFARCTION

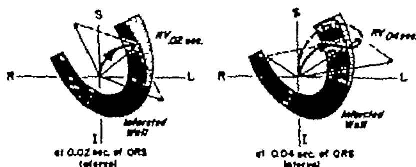


Fig. 1. The hypothesized mechanism of the QRS abnormalities in myocardial infarction. In this schematic figure the heart is shown in frontal view, the interventricular septum has been omitted for the purpose of simplification. In each part of this figure the resultant or mean instantaneous QRS vector (RV) is the resultant of two component vectors. The efferent limb of the planar QRS loop, determined by the resultant or mean 0.02-second and mean 0.04-second instantaneous vectors, is represented by a solid curved line, and the dashed line which completes the planar loop corresponds to the afferent limb of the loop. A depicts the course of events during the initial 0.04-second of the ventricular activation process in the normal heart. B demonstrates the effects of diaphragmatic infarction on the resultant vectors and planar QRS loop. Note that the resultant vectors in this part of the figure are obtained by vector addition of the preinfarction resultant vectors and component vectors equal in magnitude but opposite in direction to those normally produced by the infarcted wall of the left ventricle.

and a Q wave in Lead aVF satisfying either of the criteria of width and depth just described, preferably both.[4]

B. Posterolateral myocardial infarction: an R wave in Lead V_1 of 0.04-second or more duration and an R/S amplitude ratio in that lead equal to or exceeding 1, and a Q wave in Lead V_6 with a width of 0.04 second or more and a depth exceeding 15 per cent of the total QRS amplitude in this lead.[4] (This latter criterion was considered to be optional and was not satisfied in all electrocardiograms in the cases of posterolateral myocardial infarction.)

C. Diaphragmatic posterolateral infarction: the combined criteria listed above for the preceding two types of inferoposterior myocardial infarction.[4]

D. Strictly posterior myocardial infarction: the presence in Leads V_{3R} or V_1 of any of the following QRS configurations—rSR', a notched or slurred R, or an RS configuration with an R/S amplitude ratio equal to or greater than 1.

Table I The extreme usual and average orientations of the mean 0 02 second maximal mean† and terminal mean‡ instantaneous vectors of the QRSsE loop in 100 normal vectorcardiograms recorded with the Frank lead system*

	Horizontal			Right sagittal			Frontal		
	Usual	Average	Extreme	Usual	Average	Extreme	Usual	Average	Extreme
Mean 0.02-second instantaneous QRS vector	+30° to +95°	+60°	0° to +110°	−15° to +50°	+15°	−30° to +90°	+5° to +50°	+30°	−25° to +100°
Maximal mean instantaneous QRS vector	−10° to +20°	+5°	−25 to +30°	+65° to +115°	+90°	+55° to +130°	+20° to +50°	+35°	+15° to +55°
Terminal mean instantaneous QRS vector	−120° to −60°	§	−150° to 0°	+110° to −150°	§	+90° to −110°	−90° to +30°	§	+20° to −20°

*Range of variation in orientation in 85 per cent of the vectorcardiograms
†Corresponding approximately to the mean 0 04 second instantaneous QRS vector
‡Corresponding approximately to the mean 0 06-second instantaneous QRS vector
§Because of the extremely wide range of variation in orientation of the terminal mean instantaneous QRS vector the average orientation of this vector is not listed because it would have little significance
Note The order in which the range of variation in orientation of a given vector is given in degrees is such that the range in orientation is meant to be read in a clockwise direction in any given plane of projection.

Table II Orientation of the mean 0 02 second and maximal mean instantaneous vectors of the QRSsE loop in diaphragmatic myocardial infarction

	Horizontal			Right sagittal			Frontal		
	Usual	Average	Extreme	Usual	Average	Extreme	Usual	Average	Extreme
Mean 0 02-second instantaneous QRS vector	−10° to +90°	+55°	−20° to +150°	−120° to −10°	−70°	0° to −180°	−130° to 0°	−80°	+5° to −150°
Maximal mean instantaneous QRS vector	−50° to +20°	−40°	−100° to +20°	+110° to −150°	+170°	+80° to −100°	−10° to +30°	+15°	−100° to +60°

All of the vectorcardiograms included in this study series were recorded with the corrected lead system of Frank.[4] The left sagittal projections of vectorcardiograms obtained with the Frank lead system have been transposed into their mirror-image right sagittal counterparts. Reference frames for each planar projection of the vectorcardiogram are depicted in Fig 2 It should be noted that when the range of variation in orientation of a vector in a given projection of the vectorcardiogram is cited the range in degrees is expressed so as to read in a clockwise direction in the appropriate reference frame In evaluating the QRSsE loops in the vectorcardiograms in inferoposterior myocardial infarction the authors preferred to adopt a semiqualitative approach rather than a strictly quantitative approach since this seemed to offer certain practical advantages and at the same time did not seem to present any significant handicap in the interpreting of these vectorcardio-

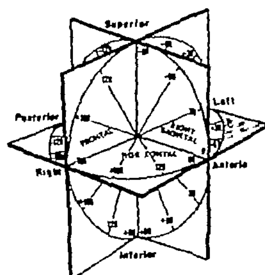


Fig. 2. Planar reference frames for the vectorcardiographic QRSsÊ loop, as if viewed from the right, anterior, and slightly superior. Note that the right sagittal plane, rather than the left sagittal, is utilized in this study.

grams. Thus, no effort was made to measure accurately the magnitude of the vectors although this was assessed in a qualitative way. In the main, the following features of the planar QRS loops of the vectorcardiograms in cases of inferoposterior myocardial infarction and of a control group of vectorcardiograms were studied: (1) the orientations of the mean 0.02 second and maximal mean instantaneous vectors of the planar QRS loops, (2) the direction of inscription of the planar QRS loops, and (3) the presence or absence of an abnormal concavity in the efferent or afferent limbs of the planar QRS loops.

Results

Normal control vectorcardiograms (100 cases). The specific findings in the normal control vectorcardiograms which are represented in Table I and Fig. 3 can be summarized as follows: (1) Normally, the initial deflection of the QRSsÊ loop was written to the right anteriorly and either inferiorly or superiorly and in a given planar projection generally had the same direction of inscription as the QRS loop itself. (2) The mean 0.02-second instantaneous vector of the QRSsÊ loop generally occupied the left anterior and inferior octant. (3) The maximal mean instantaneous vector of the QRSsÊ loop was normally oriented inferiorly to the left and either slightly anteriorly or slightly posteriorly. (4) The horizontal QRS loop of the normal vectorcardiogram was invariably inscribed counterclockwise and the right sagittal loop was invariably inscribed clockwise. The frontal QRS loop in general tended to be inscribed counter

Table III. Orientation of the mean 0.02 second, maximal, and terminal mean instantaneous vectors of the QRSsÊ loop in posterolateral myocardial infarction

	Horizontal			Right sagittal			Frontal		
	Usual	Average	Extreme	Usual	Average	Extreme	Usual	Average	Extreme
Mean 0.02-second instantaneous QRS vector	+140° to +100°	+110°	+140° to +80°	−20° to +30°	+10°	−20° to +60°	+80° to −140°	180°	+10° to −90°
Maximal mean instantaneous QRS vector	0° to +100°	+50°	−10° to +130°	0° to −160°	+65°	−10° to −140°	0° to +60°	+25°	0° to −120°
Terminal mean instantaneous QRS vector	−150° to −30°	†		+150° to −90°	†		180° to +40°	†	

*The extreme range of variation in orientation of the terminal instantaneous vector of the QRSsÊ loop is not presented in this instance because of the wide limits of variation.

†Because of the extremely wide range of variation in orientation of the terminal mean instantaneous QRS vector, the average orientation of this vector is not listed because it would have little significance.

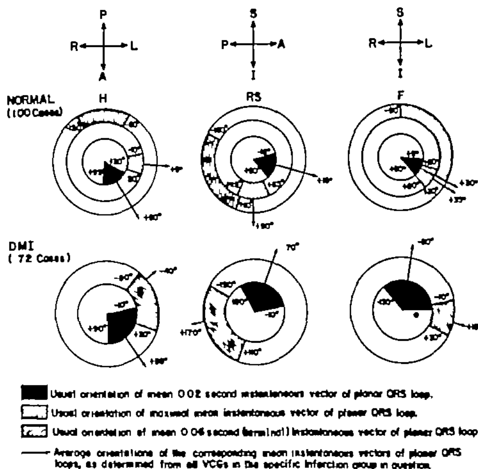


Fig. 3. The usual range and average orientations of the mean 0.02-second and maximal mean instantaneous vectors of the QRSsÊ loop in normal vectorcardiograms and vectorcardiograms of diaphragmatic myocardial infarction (*DMI*). The usual range and average orientations of the mean 0.06-second instantaneous vector of the QRSsÊ loop are shown only for the normal control group of vectorcardiograms. *H*, Horizontal projection. *RS*, Right sagittal projection. *F*, Frontal projection.

clockwise the more nearly its maximal vector paralleled the 0 degree axis, and to be inscribed clockwise the more nearly its maximal vector approached the +90 degree axis. (5) The efferent or outgoing limb of the QRSsÊ loop was usually outwardly convex, whereas the afferent limb was less consistently outwardly bowed.

Diaphragmatic myocardial infarction (72 cases). Infarction of the diaphragmatic or inferior wall of the left ventricle leads to a predominance of electrical forces directed superiorly and these unbalanced forces are present during the first 0.04-second of ventricular activation. Thus as one might anticipate the abnormal superiorly directed QRS forces in diaphragmatic infarction affect the vectorcardiographic QRSsÊ loop principally in its right sagittal and frontal projections. The QRSsÊ loop findings observed in the vectorcardiograms in cases of diaphragmatic myocardial infarction were as follows (Table II and Figs. 3 and 4). (1) The mean 0.02-second instantaneous vector of the QRSsÊ loop was deviated superiorly. Its average orientation in the horizontal projection was +55 degrees, in the right sagittal projection −70 degrees (normal +15 degrees) and in the frontal projection −80 degrees (normal +30 degrees). Although there was some overlapping of the extreme ranges of variation in orientation of the mean 0.02-second instantaneous QRS vectors in the right sagittal and frontal projections of normal vectorcardiograms and of those

which showed diaphragmatic myocardial infarction there was no overlapping of the usual range of variation in orientation of this vector.* (2) The mean maximal instantaneous QRS vector tended to occupy a more posterior and less inferior orientation in diaphragmatic myocardial infarction than normally but this feature was not found to be useful diagnostically. The average orientation of the mean maximal instantaneous vector was −40 degrees in the horizontal projection (normal +5 degrees) +170 degrees in the right sagittal projection (normal +90 degrees) and +15 degrees in the frontal projection (normal +35 degrees). There was significant overlapping of the extreme and to a lesser extent the usual ranges of orientation of the mean maximal instantaneous QRS vector in the vectorcardiograms of diaphragmatic myocardial infarction and in normal vectorcardiograms. (3) In almost one half of the vectorcardiograms of patients with diaphragmatic infarction there was some abnormality in the direction of inscription of the right sagittal projec

*"Usual" range of orientation is the range in 85 per cent of the cases.

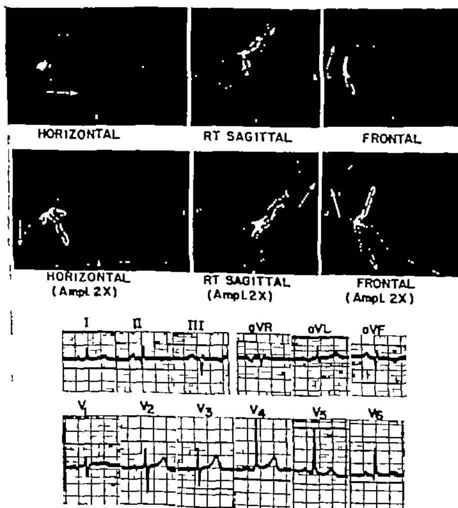


Fig 4 Electrocardiographic and vectorcardiographic findings in a patient with a recent diaphragmatic myocardial infarction. Note the large superiorly directed early deflection of the right sagittal QRS loop and the reversed inscription of the frontal QRS loop. These findings are indicative of diaphragmatic infarction whereas the superiorly directed TsÊ loop is compatible with diaphragmatic ischemia. There is no S-T vector

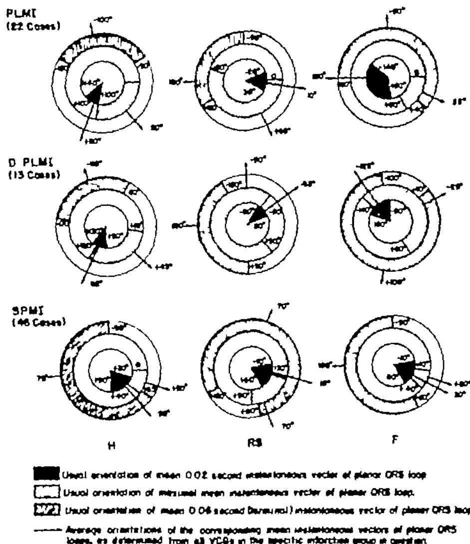


Fig. 5. The usual range and average orientations of the mean 0.02-second, maximal mean, and mean 0.06-second instantaneous vectors of the QRS-Ê loop in vectorcardiograms of posterolateral (*PLMI*), diaphragmatic-posterolateral (*D-PLMI*), and strictly posterior myocardial infarction (*SPMI*).

tion of the QRS-Ê loop. Thus, in about one sixth of the cases the loop was inscribed entirely counterclockwise. In over 25 per cent of the cases the right sagittal loop was inscribed counterclockwise/clockwise. *In almost 20 per cent of the cases* the proximal portion of the loop was inscribed clockwise and the distal portion was inscribed counterclockwise. In the remaining third of the vectorcardiograms the right sagittal loop was inscribed entirely clockwise. In over 50 per cent of the vectorcardiograms of diaphragmatic infarction the frontal QRS loop was inscribed entirely clockwise whereas in almost an additional one third of the cases the proximal portion of the frontal loop was inscribed clockwise and the distal portion was inscribed counterclockwise. In the other 7 cases out of the total group *with counterclockwise inscribed frontal* loops the efferent limb of the loop was invariably bowed superiorly, usually with clockwise inscription of its initial deflection.

Posterolateral myocardial infarction (22 cases). Infarction which involves the posterolateral wall of the left ventricle is characterized by unbalanced QRS forces which are directed anteriorly and to the

right and are responsible for the following changes in the QRSsÊ loop (Table III and Figs. 5 and 6) (1) The mean 0 02 second instantaneous QRS vector was observed to be displaced to the right and anteriorly its average orientation was +110 degrees in the horizontal projection (normal +60 degrees) and 180 degrees in the frontal projection (normal +30 degrees) Again there was slight overlapping of the extreme ranges of variation of orientation of the mean 0 02-second instantaneous vectors in the vectorcardiograms of posterolateral myocardial infarction and in the corresponding normal vectorcardiograms, but this was of even less significant degree than in the vectorcardiograms of diaphragmatic infarction Moreover the relative magnitude of the anterior component of the mean 0 02-second instantaneous vector in posterolateral myocardial infarction seemed to be greater than in the normal control group of vectorcardiograms.

(2) There was significant anterior and medial displacement of the maximal mean instantaneous QRS vector in posterolateral myocardial infarction the average orientation of this vector in the horizontal projection was +50 degrees (normal +5 degrees) and in the frontal projection +85 degrees (normal +35 degrees) In only 2 of the 22 cases of posterolateral myocardial infarction was the horizontal QRS loop (or its proximal portion) inscribed clockwise. In 3 of the vectorcardiograms the proximal part of the horizontal QRS loop was inscribed counterclockwise and the distal portion was inscribed clockwise. It is of interest that in 4 of the 22 vectorcardiograms the right sagittal QRS loop (or its proximal portion) was inscribed counterclockwise

Diaphragmatic posterolateral myocardial infarction (13 cases) The QRSsÊ loop in vectorcardiograms of cases of combined diaphragmatic posterolateral myocardial

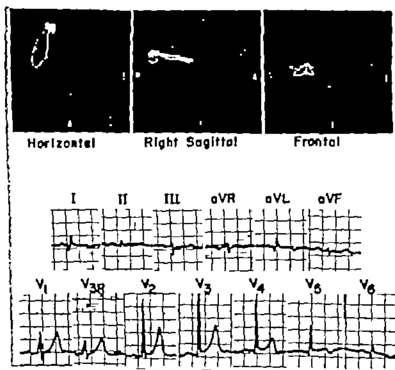


Fig 4 The electrocardiogram and vectorcardiogram in recent posterolateral myocardial infarction. The mean 0 02-second instantaneous vector of the horizontal QRS loop is oriented at about +130 degrees in the horizontal reference frame, and the long axis or maximal mean instantaneous QRS vector is displaced markedly anteriorly and medially in the horizontal plane The large rightwardly and anteriorly directed TsÊ loop in the horizontal plane is compatible with posterolateral myocardial ischemia.

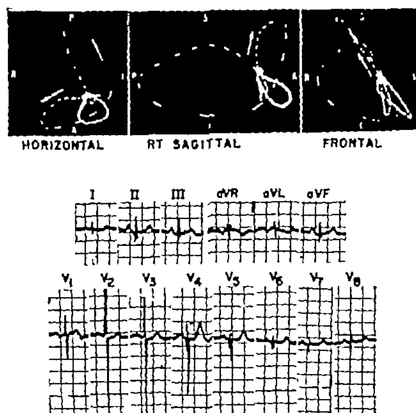


Fig 7 Electrocardiographic and vectorcardiographic findings in old diaphragmatic-posterolateral myocardial infarction. The characteristic findings of each component type of infarction are quite distinctive and easily recognizable.

infarction showed the features distinctive of each of the two component types of infarction (Table IV and Figs. 5 and 7)

1 The mean 0.02-second instantaneous QRS vector was directed on the average along the +115 degree axis in the horizontal projection along the −35 degree axis in the right sagittal projection and along the −125 degree axis in the frontal projection

2 The average orientations of the maximal mean instantaneous QRS vectors of the planar QRS loops were +45 −90 and +120 degrees, in the horizontal right sagittal and frontal projections of the vectorcardiogram respectively

3 *In 5 of the 13 vectorcardiograms the* horizontal QRS loop was inscribed entirely clockwise in 3 of the vectorcardiograms the right sagittal projection (or its proximal portion) was inscribed counterclockwise and in 11 of the 13 vectorcardiograms the frontal QRS loop (or its proximal portion) was inscribed clockwise.

4 In general it can be said that the single most characteristic feature of the QRSsÊ loop in combined diaphragmatic posterolateral myocardial infarction is the presence of an abnormally large early deflection of the loop to the right anteriorly and superiorly

Strictly posterior myocardial infarction (46 cases)

1 The mean 0 02-second instantaneous vector of the QRSsÊ loop was not significantly displaced in most of the vectorcardiograms its average orientation was +50 degrees in the horizontal projection +15 degrees in the right sagittal projection and +30 degrees in the frontal projection (Table V and Figs. 5 and 8)

2 On the other hand the maximal mean instantaneous QRS vector frequently tended to be oriented slightly more anteriorly than in normal vectorcardiograms. The average orientation in the horizontal projection was observed to be +20 degrees in the right sagittal projection, +70

degrees and in the frontal projection +20 degrees.

3 Even more striking in the frequency of its presence was a terminal deflection of the QRSsÊ loop the maximum instantaneous vector of which was oriented at about +175 degrees in the horizontal projection (normal approximately −80 degrees) at about −70 degrees in the right sagittal projection (normal −170 degrees) and at 180 degrees in the frontal projection (normal about −60 degrees)

4. As a general rule the horizontal QRS loop in strictly posterior myocardial infarction showed at the least anterior bowing of its afferent limb and a right posterior terminal deflection.

5 Three points which should be stressed in regard to the QRSsÊ loop in strictly posterior infarction are listed below

A Strictly posterior infarction is characterized primarily by a change in the second half of the QRSsÊ loop. Inasmuch as the posterobasal wall of the left ventricle normally is activated quite late in the QRS interval it is possible that infarction of this region of the heart has its electrical effects deferred to a correspondingly later period of the ventricular activation sequence. On the other hand an intraventricular conduction defect produced by the infarction cannot be excluded as an alternative explanation for the delayed abnormalities of the QRSsÊ loop in this type of infarction.

B Although not infrequently the long axis of the QRSsÊ loop (i.e. the maximal mean instantaneous or mean 0 04-second vector) may be rotated anterior to its normal orientation the main diagnostic change consists more often than not of one or a combination of the following findings anterior bowing of the afferent limb of the loop a right posterior terminal deflection or a partial or complete change in direction of inscription of the QRSsÊ loop in the horizontal and/or right sagittal projection

C. Approximately 50 per cent of the horizontal QRS loops (14 of the 46 cases of strictly posterior infarction) exhibited either a clockwise or clockwise/counterclockwise direction of inscription whereas an additional 20 per cent of the cases displayed horizontal QRS loops with a coun

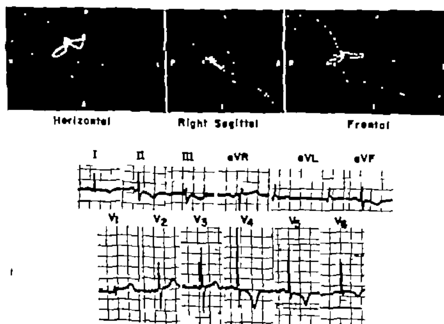


Fig 8 The electrocardiogram and vectorcardiogram in a recent strictly posterior myocardial infarction. Note that the main QRSsÊ-loop abnormalities of diagnostic importance involve the afferent limb and terminal portion of the loop. Thus, there is anterior displacement of the afferent limb of the horizontal QRS loop and a clockwise-inscribed terminal deflection of the loop to the right, posteriorly and superiorly

Table IV. Orientation of the mean 0.02 second, maximal, and terminal mean instantaneous vectors of the QRSsÊ loop in diaphragmatic posterolateral myocardial infarction

	Horizontal			Right sagittal			Frontal		
	Usual	*Average*	*Extreme*	*Usual*	*Average*	*Extreme*	*Usual*	*Average*	*Extreme*
Mean 0.02-second instantaneous QRS vector	−90° to −130°	−115°	−90° to −190°	−60° to −70°	−35°	− 0° to −20°	−160° to −90°	−1 5°	−170° to −80°
Maximal mean instantaneous QRS vector	−10° to −170°	−45°	−30° to −130°	−50° to −50°	−90°	−40° to −50°	−140° to −60°	−25°	−150° to +60°
Terminal mean instantaneous QRS vector	−170° to −60°	†		−90° to −170°	†		−40° to −100°	†	

*The extreme range of variation in orientation of the terminal instantaneous vector of the QRSsÊ loop is not presented because of the wide limits of its variation.

†Because of the extremely wide range of variation in orientation of the terminal mean instantaneous QRS vector, the average orientation of this vector is not listed because it would have little significance.

Table V. Orientation of the mean 0.02 second, maximal, and terminal mean instantaneous vectors of the QRSsÊ loop in strictly posterior myocardial infarction

	Horizontal			Right sagittal			Frontal		
	Usual	*Average*	*Extreme*	*Usual*	*Average*	*Extreme*	*Usual*	*Average*	*Extreme*
Mean 0.02-second instantaneous QRS vector	−70° to +90°	−90°	−5° to −100°	−10° to −60°	−15°	−40° to −95°	−10° to +60°	+30°	−30° to +80°
Maximal mean instantaneous QRS vector	0° to −40°	−20°	−10° to −90°	−70° to +90°	− 0°	−5° to −190°	+10° to +40°	−20°	−70° to +60°
Terminal mean instantaneous QRS vector	−35° to −97°	−1 5°		−190° to −80°	−70°		−60° to −90°	180°	

*The extreme range of variation in orientation of the terminal instantaneous vector of the QRSsÊ loop is omitted because of the wide limits of its variation.

terclockwise clockwise inscription. In the right sagittal projection the QRS loop in 8 of the 46 cases had an entirely clockwise inscription, and 7 cases showed a clockwise counterclockwise direction of inscription.

Discussion

The observations just reported in this vectorcardiographic study indicate that the various types of inferoposterior infarction are characterized by deviation of certain mean instantaneous vectors of the QRSsÊ loop away from the effective electrical site of the infarction. As one might anticipate, the mean instantaneous vectors of the QRSsÊ loop which are affected by an infarction are those which appear during that portion of the QRS interval when the infarcted heart muscle normally undergoes

activation Moreover the postinfarction mean instantaneous vectors of the QRSsÊ loop generally acquire not only an abnormal direction but also an increased magnitude as well

The mean 0 02-second instantaneous vector of the QRSsÊ loop is the vector which is primarily affected in the various types of inferoposterior infarction whereas the maximal or mean 0 04-second vector less frequently exhibits diagnostic changes. The principal exception to the previous statement is the case of strictly posterior myocardial infarction which is characterized vectorcardiographically by abnormalities of the later portions of the QRSsÊ loop Two alternative explanations for this finding were cited earlier in this paper

Summary

1 The QRSsÊ-loop findings have been described in vectorcardiograms recorded with the Frank lead system from 100 subjects without clinically detectable heart disease and from 153 patients with inferoposterior myocardial infarction

2 In the vectorcardiograms of cases of diaphragmatic (inferior) posterolateral and diaphragmatic-posterolateral infarction the abnormality most consistently observed was deviation of the mean 0 02 second instantaneous vector and to a lesser extent the maximal or mean 0 04-second instantaneous vector of the planar QRS loops away from the effective electrical site of the infarction.

3 In cases of strictly posterior infarction the QRSsÊ loop displayed an anterior deviation of the maximal or mean 0 04-second and subsequent instantaneous QRS vectors.

REFERENCES

1 Grant, R P and Murray R H. QRS complex deformity of myocardial infarction in the human subject, Am. J Med. 17:587 1954

2. Gardberg, N and Levy L I and II—The QRS complex of the electrocardiogram in myocardial infarction, with remarks on methods of recording, Am Heart J 51:501 and 654 1956.

3 Grishman, A., and Scherlis, L. Spatial vectorcardiography Philadelphia, 1952, W B. Saunders Company

4. Massie, E and Walsh, T J Clinical vectorcardiography and electrocardiography Chicago, 1960, The Year Book Publishers, Inc.

5 Goldberger E. Unipolar lead electrocardiography and vectorcardiography ed. 3, Philadelphia, 1953, Lea & Febiger

6. Frank, E. An accurate clinically practical system for spatial vectorcardiography Circulation 13:736, 1956.

Studies with tritiated digoxin in human subjects after intravenous administration

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Digitoxin labeled with carbon 14 has been the subject of a number of studies in recent years[1-4] and much information has accumulated in regard to the metabolic behavior of this long-acting glycoside in the human body. Until recently, similar studies with digoxin have not been possible because of the expense and difficulty of obtaining a C^{14} label. The possibility of a radiohydrogen or tritium label was explored and found to be both cheap and practical. A previous report of studies in which tritium-labeled digoxin was utilized described the serum levels and excretion after oral administration of the glycoside.[5] The purpose of the present study was to obtain similar information after intravenous administration of tritium-labeled digoxin.

Methods

Tritium-labeled digoxin was prepared by the Wilzbach hydrogen exchange method* and radioactive impurities and by-products were removed by column partition chromatography.† The purified product was supplied in ampules of 1 mg. of tritiated digoxin in 1 c.c. of 95 per cent alcohol. Assays revealed a specific radioactivity of 44 μc per milligram of tritiated digoxin.

Thirteen hospitalized adult male patients were selected for study: 11 had congestive heart failure and 2 had cardiac arrhythmias. The subjects were given 0.5 to 1.0 mg. of tritiated digoxin diluted with 10 c.c. of normal saline intravenously over a period of 2 minutes. Zero time was the time of onset of the injection. Specimens of venous blood were obtained from the opposite antecubital vein at 3, 6, 9, 12, 15, 20, 25, 30, and 45 minutes, and at 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 6, 7, 8, 10, 12, and 24 hours, and daily thereafter for 7 to 10 days. Specimens were allowed to clot and were centrifuged. The serum was separated and refrigerated.

Specimens of urine were collected every 4 hours during the first 24 hours, every 12 hours on the second day, and daily thereafter for 7 to 10 days. Stools were collected daily for 7 to 10 days.

All specimens were prepared for analysis in a similar manner. An aliquot of each was shaken with chloroform in a separatory funnel. The chloroform was then passed through an activated alumina column, 100 to 200 mesh, 0.5 cm. in diameter and 5 cm. in height. The chloroform was discarded. Twenty milliliters of 2:1 chloroform-ethanol were run through the column, collected

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Table I. Clinical information and serum half-times

Patient	Age	Race, sex	Weight (pounds)			Diagnosis†	B		C
			Before digoxin	After digoxin	Gain or loss		Minutes	Hours	Minutes
1. H.I.	70	N,M	96.5	97.0	+ 0.5	ASHD	1 600	26.6	23
2. M.C.	66	W,M	151.0	150.0	− 1.0	ASHD	2 650	44.1	42
3. J.D.	73	N,M	175.5	175.0	− 0.5	HCVD	3 300	55.0	36
4. C.O.	57	W,M	150.0	155.0	+ 5.0	PAT of unknown etiology	650	10.8	27
5. J.J.	29	N,M	179.0	172.0	− 7.0	ASHD	2 100	35.0	30
6. E.F.	58	W,M	130.0	126.0	− 4.0	HCVD	2 300	38.3	24
7. A.J.	60	N,M	152.0	141.0	−11.0	Syphilitic HD	1 800	30.0	28
8. G.H.	73	W,M	162.0	158.5	− 3.5	HCVD	2 070	34.5	36
9. D.O.	73	W,M	142.5	133.0	− 9.5	RHD	3 050*	50.8	48
10. C.C.	68	N,M	168.0	147.0	−21.0	HCVD	1 900*	31.6	55
11. C.L.	37	W,M	173.0	164.0	− 9.0	Undiagnosed HD	2 400	40.0	23
12. C.A.	65	N,M	171.0	168.5	− 2.5	HCVD	1 720	28.6	34
13. C.J.	52	W,M	128.0	123.5	− 4.5	RHD	1 610	26.8	32
Mean	60		152.2	147.0	− 3.2		2 018	33.6	30.4

*Not included in the mean.
†ASHD: Arteriosclerotic heart disease. HCVD: Hypertensive cardiovascular disease. PAT: Paroxysmal auricular tachycardia. HD: Heart disease. RHD: Rheumatic heart disease.

and evaporated to dryness. A scintillation counting solution was added to the residue. This method satisfactorily removed most of the color and impurities which cause quenching or reduction of counting rate in the liquid scintillation counter. Specimens were counted in a Packard Tri-Carb liquid scintillation counter. All counting rates were corrected for quenching by adding a known amount of tritium and recounting. Ninety-six per cent of a known quantity of digoxin was recovered when passed through this system.

Chromatography was employed to ascertain the purity of the tritiated digoxin. A sample of material was placed on Whatman No. 1 filter paper impregnated with 30 per cent formamide in acetone. The solvent system utilized contained chloroform 78 parts, benzene 12 parts, and butanol 5 parts saturated with formamide. Fig. 1 shows a radiochromatogram of Lot T 333 of digoxin used in this study and illustrates the purity of the compound. In order to exclude the possibility of the presence of tritiated water, samples of the compound were evaporated to dryness, reconstituted and recounted without significant alteration in counting rates. Samples of urine were subjected to chromatography in the same manner in order to identify the radioactivity present.

Analysis of data

A summary of clinical information (diagnosis, age, weight, sex, and race) and serum half-times is shown in Table I. All the patients except 2 were in congestive heart failure. All except 2 exhibited loss of weight with administration of digoxin. Signs of congestive failure, such as tachycardia, pulmonary râles, edema, etc., were noted to improve in all patients with congestive heart failure.

The term *half-time* or *half-life* as used in the remainder of this paper refers to the time required for one half of the radioactivity originally present to disappear.

Fig. 2 demonstrates a composite graph of the serum turnover curves of 11 patients. The 3-minute specimen is shown as 100 per cent; the remaining points are expressed as per cent of this figure so as to avoid quantitative differences in the patients due to weight, dose, etc. The per cent count is plotted against time on semilogarithmic graph paper.

Radioactivity is present in the first specimen 3 minutes after onset of injection and falls rapidly during the first 20 to

Fig. 1. Gas-flow radiochromatogram of digoxin. Lot T 333 used in these experiments. The origin is marked on the right as O and represents the area where 968,000 counts of tritium-labeled digoxin were applied. A full-scale deflection on this graph represents 1,000 counts, and, because the gas-flow counting apparatus is approximately 1 per cent efficient, the observed peak represents practically all the radioactivity applied to the strip and demonstrates the radiochemical purity of this lot of digoxin.

25 minutes and more gradually for the next 150 to 240 minutes. A plateau curve is then obtained which declines gradually over a period of several days.

Inspection of Fig. 2 reveals that the serum radioactivity curve may be divided into three exponential curves. Curve *A* is the plot of the per cent counting rates. Curve *B* is the best straight line which can be drawn after the equilibration plateau is obtained. Curve *C* is obtained by subtracting Curve *B* from *A* and a steeper slope is observed for this exponential. Curve *D* is a still earlier and steeper curve obtained by subtracting Curve *C* from the actual plotted points.

Curve *B* represents the equilibration plateau or dominant half-life of digoxin. It is believed to reflect metabolism and excretion of digoxin, with the slow disappearance from the sera after the equilibration plateau is achieved being a function of release from the tissue and elimination from the body via the urine and stool. Curve *C* probably represents the phase of tissue distribution and binding since this rapid disappearance cannot be explained by excretion because this portion of the curve has been excluded.

The "half-life" of these curves is a useful temporal function which may be utilized to illustrate the clinical correlation that can be established by the digoxin serum radioactivity curve. Curve *B* which represents metabolism and excretion has a half life of 33.3 hours and shows the relatively rapid disappearance of digoxin through metabolism and excretion. One half of the original dose requires this length of time for disappearance from the serum and since this portion of the radioactivity curve is a function of metabolism and excretion, the rate of decline follows the loss of therapeutic activity.

Curve *C* of tissue distribution and binding shows a half life of 30 minutes; one half of the original dose disappears to be distributed and bound in the tissues (metabolism and excretion theoretically eliminated). This is consistent with the rapid onset of clinical effect when this glycoside is given intravenously because a therapeutic effect is usually present within 30 minutes after administration. It should be recognized that the distribution of digoxin in different tissues is highly selective.[9]

Curves *B* and *C* were constructed for each individual patient and the values obtained are shown in Table I. Two patients (D. O. and C. C.) do not represent truly valid intravenous studies because there was subcutaneous extravasation dur

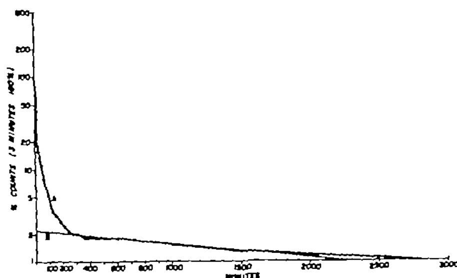


Fig 2A. Serum turnover curve of digoxin after intravenous administration. This figure is a composite graph of the curves of 11 patients per cent counts are plotted against time on a semilogarithmic scale. Curve *A* is the plot of actual counts Curve *B* is the best straight line after the equilibration plateau has been reached, extrapolated to zero time. Curve *B* represents metabolism and excretion of digoxin and has a half-life of 33.3 hours.

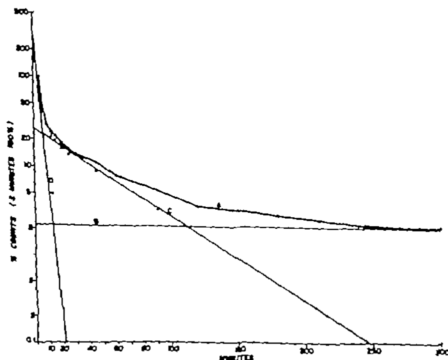


Fig 2B An enlargement of the early portion of Fig 2A to illustrate the exponential Curves *B* *C*, and *D* Curve *A* is the plot of original counts. Curve *B* is the best straight line after the equilibration plateau has been reached extrapolated to zero time. Curve *C* is the phase of tissue distribution and binding; it is obtained by subtracting Curve *B* from the actual counts (*A*) and has a half-life of 30 minutes. Curve *D* represents serum distribution and is obtained by subtracting Curve *C* from the actual count It has a half-life of about 2 minutes.

Table II Excretion of digoxin

Patient	Dose of digoxin (mg.)	Microcuries administered	Excretion in urine, Per cent of total dose administered: Days 1	2	3	3-Day total	5-Day total	7 Day total	Urine half time (days)	Renal plasma clearance	Excretion in stools, Per cent of total dose administered: Days 3	5	7
1. H.I.	0.5	22	20.1‡	13.1	5.9	39.1‡	42.8‡	46.4‡	1.6	§	‡	‡	‡
2. M.C.	1.0	44	32.5	11.0	10.1	53.6	65.1	‡	—	§	5.2	5.2	7.3
3. J.O.	1.0	44	31.4	10.3	9.7	51.4	64.4	71.7	2.2	§	1.0	1.6	6.2
4. C.O.	1.0	44	39.4	13.1	8.9	61.4	73.0	79.1	1.5	§	0.9	8.2	9.3
5. J.J.	1.0	44	48.3	13.2	6.7	68.2	75.6	78.4	1.4	150.33	11.7	14.2	14.3
6. E.F.	1.0	44	29.0	14.0	10.7	53.7	67.8	73.9	2.5	94.58	1.2	13.4	16.9
7. A.J.	1.0	44	43.4	19.2	15.8	78.4	90.3	96.6	1.5	84.69	5.2	6.2	8.0
8. G.H.	1.0	44	35.5	14.2	8.6	58.3	70.0	75.5	1.9	70.39	4.6	15.7	16.9
9. D.O.	1.0	44	33.4	14.9	11.8	60.1	76.0	83.0	2.6	64.23	4.5	11.5	17.4
10. C.C.	1.0	44	26.3	10.6	9.5	46.4	61.1	66.3‡	1.4	68.14	8.4	12.6	13.7
11. C.L.	1.0	44	46.4	16.6	8.9	71.9	83.6	89.4	1.6	117.11	4.0	8.5	10.1
12. C.A.	1.0	44	36.5	13.2	10.3	60.0	69.9	76.0	2.2	80.61	2.8	11.3	13.4
13. C.J.	1.0	44	37.5	12.8	8.2	58.5	69.9	76.2	1.8	78.48	5.0	7.5	7.5
Mean			38.1	14.2	10.0	62.2	70.0	80.0	1.85	90.30	8.7	9.7	11.8

*Not included in the mean.
†Expressed as milliliters of plasma cleared of digoxin per minute; average values for the first 2,520 minutes of study.
‡Incomplete collection.
§Data inadequate for calculation.

ing the injection and data from these patients are not included in the mean of the curves nor are they included in Fig. 2.

The mean half time of Curve *C* is 30.4 minutes (23 to 42) and that of Curve *B* is 33.6 hours (10.8 to 55). Variation of the magnitude observed in the turnover curves of these patients is consistent with differences usually seen clinically in dose requirement. Curve *D* demonstrates a consistent half time of about 2 to 4 minutes; these figures are not shown because no correlation can be established other than rapid distribution in the serum and it depends on such variables as blood volume, rapidity of injection, cardiac output, etc. On the assumption that none of the digoxin left the serum during the first few minutes, values (counting rates) 4 to 6 times those observed per milliliter of serum should have been demonstrated.

A summary of the studies of excretion is shown in Table II. This table illustrates the very rapid excretion of digoxin in the urine during the first day after intravenous administration. Twenty to 48 per cent of the total amount administered is excreted in the first 24 hours. The 7-day total excretion varied from 72 to 97 per cent in those patients with complete studies. Urine half times are also shown and illustrate the disappearance of one half of the radioactivity initially present in an average of 1.85 days. Note that this figure is reasonably close to the serum digoxin half time and tends to support the impression that the dominant portion of the serum curve (Curve *B*) is associated with metabolism (release) and excretion.

Paper chromatography was used to search for radioactive metabolites in specimens of urine. Virtually all of the radioactivity was present in the area which contained digoxin. A previous study[1] demonstrated only a very small portion of total radioactivity (2 per cent) separate from the digoxin chromatographic band on pooled urine specimens after oral administration of digoxin. Distinct identification of metabolites was not accomplished in this study. Fig. 3*A* shows a chromatogram of the urine of Patient E. F. Fig. 3*B* shows a chromatogram of pure digoxin and Fig. 3*C* shows a chromatogram of urine com

bined with pure digoxin. These illustrations show that the radioactivity found in the urine corresponds to the original sample of radiochromatographically pure digoxin. Since virtually all the radioactivity administered was recovered in urine and stools, and since the method of extraction precludes the extraction of tritiated water as a breakdown product the digoxin is thought to possess a rather stable random label with tritium

Urinary clearance of digoxin is also shown in Table II Values are expressed as milliliters of plasma cleared of digoxin per minute at the specified times shown on the table The mean for this determination is

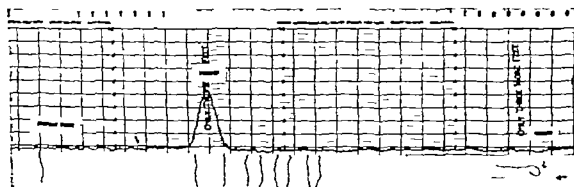


Fig. 3A Chromatogram of urine extract of Patient E.F

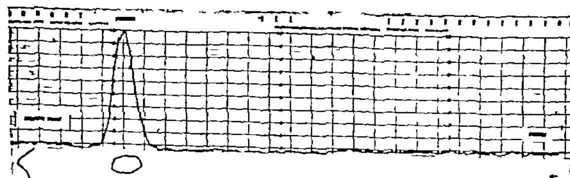


Fig 3B Chromatogram of original sample of pure digoxin.

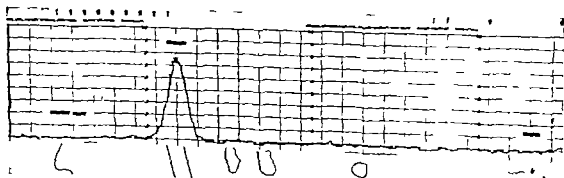


Fig 3C Chromatogram of urine extract of Patient E.F and pure digoxin. The chromatograms of Figs. 3A 3C were run simultaneously in the same solvent system and demonstrate that the radioactivity in the urine is virtually pure digoxin. Other fluorescent areas marked on the chromatograms represent nonradioactive substances found in the urine.

90.3 ml. of plasma cleared of digoxin per minute for the first 2,520 minutes after administration. We have no information relative to the mechanisms involved in the renal excretion of digoxin.

Studies of stools revealed that an average of 11.8 per cent of the tritiated digoxin administered appeared in the stools in 7 days. The range of excretion in the feces was 6.2 to 16.9 per cent of the total amount administered. Data on the excretion of digoxin in the stools are shown in Table II.

A comparison of the serum digoxin radioactivity curves found after intravenous and oral administrations is shown in Fig. 4. The per cent of digoxin present in the sera of 12 patients after oral administration[9] is compared with that in the sera of 11 patients after intravenous administration in the present series. The levels have been corrected for dose and body weight of the patients so as to obtain comparable data. Thus Fig. 4 demonstrates the differences in serum concentrations achieved by the different routes of administration. Note the higher initial serum levels and the more rapid early disappearance after intravenous administration. A later peak level and later arrival of the equilibration plateau characterize the graph of the oral study. The dominant half-life or metabolism and excretion phases of both curves are virtually identical.

Discussion

Knowledge of the fate and behavior of digoxin has been acquired through a number of excellent clinical studies.[11-14] Quantitative studies of the rate of turnover in serum and of the excretion of digoxin in urine and stools are now possible with isotope labeling techniques. Such techniques have been applied to the long-acting preparation digitoxin, and much information in regard to this glycoside has been accumulated. The study of labeled digoxin should provide similar information in regard to this preparation, which has a much shorter duration of action clinically.

The data reported here reveal that digoxin administered intravenously to patients with congestive heart failure is distributed rapidly in the blood serum with an initial serum half time of approximately 2 to 4 minutes and thereafter another more gradual slope of disappearance is detected which possesses a half time of 30 minutes, a phase which is attributed to tissue distribution and binding of the glycoside which correlate with the onset of clinical activity. A third phase of turnover is then shown which represents excretion and metabolism of the glycoside. The last phase has a half time of 33.3 hours and parallels the duration of action usually observed clinically with digoxin.

Studies of excretion reveal that most of the digoxin is removed from the body by the kidney. Twenty to 48 per cent of the administered dose was recovered in the urine in 24 hours, a mean of 38.1 per cent. Seventy-two to 97 per cent, a mean of 80 per cent, was recovered from the urine in 7 days, which demonstrates that the kidney is the major organ of excretion. This was also observed in previous studies after oral administration of tritiated digoxin.

Studies of the excretion of digoxin in the stools showed that a relatively small quantity of digoxin was excreted by this route as compared with the amount excreted by way of the kidney. An average of 11.8 per cent of the total dose administered was recovered in 7 days, the lowest observed was 6.2 per cent, and the highest was 17.4 per cent.

Comparison of the figures obtained from intravenous administration of digoxin and those obtained from oral ingestion is useful because of the information which may be deduced in regard to absorption, dosage, and clinical effect.

According to a previous publication,[9] the average 5-day excretion in the stools after administration of an oral dose of tritiated digoxin was approximately 20 per cent. The present study reveals recovery of 9.7 per cent from the stools in 5 days after intravenous administration. On the assumption that the difference between the amount of radioactivity which appears in the stools after oral and that which appears after intravenous, administration represents the digoxin unabsorbed after oral administration, 90 per cent of the oral dose is absorbed since 10 per cent could be accounted for by excretion in the stools. The variation in radioactivity noted in the stools of the group of subjects who received the drug intravenously (from 6.2

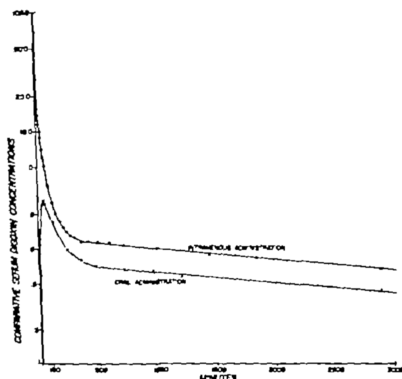


Fig. 4. Levels of digoxin in the serum after oral and intravenous administrations. The per cent of the total dose of digoxin administered per milliliter per pound of body weight $\times$ 10 is plotted against time on semilogarithmic paper. • represents the intravenous study and x represents the oral study. Note the differences in the first 400 to 500 minutes, at which time a plateau is reached.

to 17.4 per cent at 7 days) is no more than might be anticipated between different individuals.

The route of administration also leads to a striking difference in the amount of tritiated digoxin excreted in the urine. Thirty-eight per cent of the dose administered intravenously was excreted in the urine in the first 24 hours as compared with a urinary excretion of 15 per cent in 24 hours when the dose was given orally. A urinary loss of this magnitude suggests the necessity of close observation of the patient during the second day after intravenous digitalization with digoxin, since an additional maintenance dose may be necessary.

Renal plasma clearance of digoxin in this group of patients showed that 90.3 ml. of plasma was cleared of digoxin per minute. If one assumes that the normal renal plasma flow is 650 ml. per minute, about one seventh of the total was cleared of digoxin. It is probable that these patients with congestive heart failure exhibited reductions in renal plasma flow proportional to the fall in cardiac output. Ninety milliliters might represent a higher fraction of the total renal plasma flow in this group of individuals. The effect on 2 of the patients (J. J. and C. L.) is of interest. Patient J. J., a 29-year-old Negro man, had severe bilateral congestive heart failure as a result of a myocardial infarction. He exhibited good response to digitalization with a 7 pound loss of weight. Patient C. L., a 34-year-old white man, had severe heart failure on the left side with acute pulmonary edema. He also had an excellent response to digitalization. These patients had the highest values of renal plasma clearance of digoxin and at the same time they had the most severe congestive heart failure.

These patients probably demonstrate an increased glomerular filtration rate or perhaps, a direct diuretic effect described by Farber and associates[14] in studies of renal excretion after nonradioactive intravenous digoxin.

The onset of clinical activity correlates with the serum digoxin radioactivity curve very well. The curve of disappearance associated with tissue binding and distribution (Curve C) has a half life of 30 minutes in the intravenous study and 50 minutes in the oral study. These figures demonstrate the difference in onset of clinical activity after oral and intravenous administrations; disappearance of one half of the original radioactivity present parallels the usually observed onset of clinical effects in both instances. The late dominant curve of both the intravenous and oral dosages is virtually the same, 33.3 and 31.3 hours, respectively. The route of administration has no significant effect on this portion of the turnover curve.

The more rapid renal excretion after intravenous administration, 38 per cent in the first 24 hours, is probably a product of higher serum concentration after intravenous dosage and fairly high renal plasma clearance.

Summary

Thirteen patients were digitalized by the intravenous route with tritium-labeled digoxin. Radioactivity levels of the serum, urine, and stools were studied for 7 to 10 days.

Three exponential curves constructed from H³-digoxin serum levels reveal: (1) a very steep early slope of serum distribution with a half time of about 2 to 4 minutes; (2) a curve with a relatively steep slope probably representing organ distribution and tissue binding with a half time of 30 minutes; (3) a late plateau type of curve correlating with metabolism and excretion with a half life of 33.3 hours.

In the first 24 hours the renal excretion was 38 per cent of the total dose administered and 80 per cent in 7 days. Excretion in the stools was 11.8 per cent of the total dose at 7 days.

These data were compared with previously published data obtained in studies of the oral administration of H³-digoxin.

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REFERENCES

1. Sjoerdsma, A., and Fischer, C. S.: The fixation of radioactive digitoxin by isolated hearts, Circulation 4:100, 1951.
2. Okita, G. T., Kelsey, F. E., Talso, P. J., Smith, L. B., and Geiling, E. M. K.: Studies on the renal excretion of radioactive digitoxin in human subjects with cardiac failure, Circulation 7:161, 1953.
3. Okita, G. T., Kelsey, F. E., Walaszek, E. J., and Geiling, E. M. K.: Biosynthesis and isolation of carbon-14-labeled digitoxin, J. Pharmacol. & Exper. Therap. 110:244, 1954.
4. Okita, G. T., Talso, P. J., Curry, J. H., Jr., Smith, F. D., Jr., and Geiling, E. M. K.: Blood level studies of C¹⁴-digitoxin in human subjects with cardiac failure, J. Pharmacol. & Exper. Therap. 113:376, 1955.
5. Harvey, S. C., and Pieper, G. R.: Intracellular distribution of digitoxin-C¹⁴ in the heart, J. Pharmacol. & Exper. Therap. 114:14, 1955.
6. Okita, G. T., Talso, P. J., Curry, J. H., Jr., Smith, F. D., Jr., and Geiling, E. M. K.: Metabolic fate of radioactive digitoxin in human subjects, J. Pharmacol. & Exper. Therap. 115:371, 1955.
7. Okita, G. T.: Studies with radioactive digitalis, J. Am. Geriatric Soc. 5:163, 1957.
8. Spratt, J. L., and Okita, G. T.: Subcellular localization of radioactive digitoxin, J. Pharmacol. & Exper. Therap. 124:115, 1958.
9. Doherty, J. E., Perkins, W. H., and Mitchell, G. K.: Tritiated digoxin studies in human subjects, A.M.A. Arch. Int. Med. 108:531, 1961.
10. Gold, H., Cattell, McK., Greiner, T., Hanlon, L. W., Kwit, N. T., Modell, W., Cotlove, E., Benton, J., and Otto, H. L.: Clinical pharmacology of digoxin, J. Pharmacol. & Exper. Therap. 109:45, 1953.
11. Selzer, A., Hultgren, H. N., Ebnother, C. L., Bradley, H. W., and Stone, A. O.: Effect of digoxin on the circulation in normal man, Brit. Heart J. 21:335, 1959.
12. Soloff, L. A., and Zatuchni, J.: Clinical experiences with digoxin, Am. Heart J. 57:674, 1959.
13. Rose, O. A., Batterman, R. C., and DeGraff, A. C.: Clinical studies on digoxin, a purified digitalis glycoside, Am. Heart J. 24:135, 1942.
14. Farber, S. J., Alexander, J. D., Pellegrino, E. D., and Earle, D. P.: The effect of intravenously administered digoxin on water and electrolyte excretion and on renal functions, Circulation 4:378, 1951.

The calculated tempero-spatial heart vector in proved isolated left ventricular overwork

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In the last 10 years orthogonal systems of 3 leads for electrocardiography have been successfully developed.[1-4] These lead systems detect a difference in directed potentials occurring within the myocardium in such a manner that the lead axes for practical purposes may be considered to be orthogonal for all regions of the heart. This allows electrical potentials associated with the heartbeat to be accurately represented as a vector quantity in space, with the leads acting as a Cartesian reference frame. Our method is to represent graphically this vector quantity as a linear time function of its spherical coordinates. We believe that as much useful information may be derived from 3 orthogonal leads as from any other series or combination of leads recorded from the body surface. This has been supported by the recent work of Pipberger and associates.

The expression of the 3-lead potentials as a single time-varying vector quantity in space has certain theoretical advantages which should be explored. It allows an exact quantitative description of the information present in the 3-lead system at any moment as a single directed magnitude. Such a quantity lends itself to many types of analyses. Temporal relations are accurately preserved from the simultaneously recorded leads, an obstacle to interpretation which still exists in serial electrocardiography and plane projection vectorcardiography.

The present study was designed to characterize quantitatively the tempero-spatial heart vector of ventricular activation in a group of clinical conditions which singularly caused overwork of the left ventricle, to compare these results with those from a group of normal subjects, and, as a result, to derive those vectorial forces manifested on the body surface which represent the electrophysiologic changes associated with overwork of the left ventricular myocardium. These may well include the effects of hypertrophy of myocardial tissue, chamber dilatation, interstitial fibrosis, alterations in intraventricular conduction, and other unknown factors.

Method

The individual records were obtained as reported previously.[5] The lead system of Helm,[4] based on data published by Frank, was used to record simultaneously the 3 vector leads X, Y, and Z on film at a speed of 6 inches per second. The amplitudes of each lead record were then

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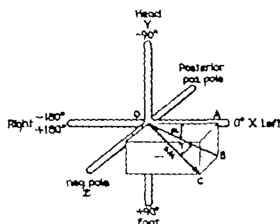


Fig. 1. The axes X, Y, and Z represent the recording or lead axes of the orthogonal lead system used and their orientation with the torso (left-right, head-foot, and anterior-posterior). The polar coordinates used to describe the heart vector are the angles alpha (α = *AOB*), tilt (*T* = *BOC*), and the scalar magnitude (*SM*) expressed in millivolts.

converted on an electronic digitizing translator* to digital data on punch cards. Readings were taken at intervals of 5 msec. throughout ventricular activation. The rectangular coordinates of the sample heart vectors thus obtained were converted to polar coordinates called *alpha*, *tilt*, and *spatial magnitude*, and the latter values were reproduced in tabular form as well as plotted individually on a time base by a Burroughs 220 electronic computer. This procedure is described in detail in another publication.[8]

The particular angles describing direction of the heart vector were chosen because of their familiarity to students of electrocardiography and vectorcardiography. As demonstrated in Fig. 1, alpha is an expression of the electrical axis of Einthoven and also the angles displayed on the frontal plane projection loops. The zero reference angle is the same in our studies as on the hexaxial reference frame. Vectors directed into the superior quadrants represent negative angles, and those directed into inferior quadrants represent positive angles. The tilt angle indicates the extent to which the spatial vector is directed anteriorly or posteriorly from the frontal plane on its axis, as described by Grant.[9] The polarity of the Z lead is such that negative angles represent anterior tilting and positive angles represent posterior tilting to the frontal plane. The range of the tilt angle thus defined is from −90 to +90, whereas the range of alpha is continuous at −180 and +180. The spatial magnitude (*SM* in Fig. 1) is the scalar magnitude of the spatial heart vector expressed in millivolts.

The spatial frequency distribution of the heart vector of ventricular activation for a group of 154 normal adults between the ages of 20 and 50 years was calculated in an earlier investigation.[10] Because of biologic variations of the heart potentials apparent with the age and sex of normal individuals, 6 subdivisions were formed on the basis of sex and decades of age. The mean of each spherical coordinate was calculated for the subgroupings, and because the scatter of each polar coordinate appeared Gaussian in distribution, normal variation was expressed as the standard deviation. Individuals of the abnormal group were then compared with individuals of the normal group corresponding to them in age and sex. Those over 50 years of age were compared with those in the 40 to 50-year subdivisions. To illustrate a typical record, the mean values of men between 30 and 40 years of age are shown against a background depicting a range of normal scatter of ±2 standard deviations (Fig. 2).

The present study is composed of 46 individuals with heart disease of the following 5 types: 14 patients with pure aortic stenosis, 12 patients with mixed lesions of aortic stenosis and aortic insufficiency, 5 individuals with pure aortic insufficiency, 7 individuals with systemic hypertension, and finally, 8 patients with pure mitral insufficiency. The diagnoses were based on a combination of clinical features, the data from cardiac catheterizations, the results of angiocardiography, and the findings at open heart operation. All individuals who had a history of myocardial infarction or clinical signs of pulmonary hypertension or right heart failure were excluded. Of those patients catheterized, none included in the study had pulmonary arterial systolic pressures greater than 45 mm. Hg. In order to exclude cases of obvious intraventricular conduction ab-

*Benson-Lehner Oscar Model K.

normalities, no patients were used who had QRS times of 0.12 second or greater.

All cases of pure aortic stenosis were proved by catheterization of the left side of the heart or by the findings made at open heart operation. Measured peak aortic valve gradients ranged from 46 to 159 mm. Hg with a mean of 91 mm. Hg. In the group with mitral insufficiency the clinical diagnosis was supported by the findings of angiography and cardiac catheterization in 6 of the 8 patients, and the diagnosis appeared to be certain on clinical grounds in the others. Again cardiac catheterization or open-heart operation supported the clinical impression in 8 of the 12 patients with mixed aortic stenosis and aortic insufficiency and angiograms confirmed the diagnosis in 2 of the group with aortic insufficiency. All others had in addition to the murmur of aortic insufficiency an abnormally wide pulse pressure which ranged from 96 to 110 mm. Hg. In order for the patients to be included in the group with systemic hypertension two criteria had to be met: a clinical record of serially elevated blood pressures for at least 1 year and a blood pressure greater than 140/100 mm. Hg at the time the record was taken. The actual range of blood pressures was from 170/110 to 250/150 mm. Hg and evidence of left ventricular enlargement on the chest film was present in 3 of the patients. In no case was the clinical electrocardiogram used as evidence of left ventricular hypertrophy. The mean age of the abnormal subjects was 41 years with a range of 21 to 64 years.

Results

When the records of the 46 abnormal subjects were compared with those of normal subjects two outstanding differences were noted. At some time during the first 40 msec. of ventricular activation the heart vector of the group with left ventricular overwork tended to be directed less anteriorly than that of the normal group shown in the tilt-angle plot. The magnitude of the heart vector during this period was normal or increased. The alpha angle demonstrated no characteristic abnormality.

During ventricular activation from 35 to 75 msec. the great majority of the abnormal group showed increases in the magnitude of the heart vector. The directions at these times were almost always normal. Whereas in normal individuals the peak or greatest spatial magnitude occurred between 35 and 50 msec., many of the group with left ventricular hypertrophy had peak magnitudes between 55 and 65 msec. As an example, the plot for a patient with pure aortic stenosis who demonstrated all of these abnormalities is shown (Fig. 2).

In order to determine the limits of the tendency of normal individuals to tilt posteriorly to the mean during the first 40 msec. we reviewed the tilt angles of the normal group of 154 and tabulated the number of sample vectors which fell 1½ to 2, 2 to 3, and 3 to 4 standard deviations posterior to the means of the group. Likewise, for the tendency of normal individuals to show increases in spatial magnitude of the sample vectors from 35 to 75

Table I. Comparison of abnormal group with the criteria of abnormality

Clinical diagnosis	*Number of cases*	*Abnormal posterior tilt*	*Abnormal spatial magnitude*	*Both abnormalities*	*Posterior tilt only*	*Spatial magnitude only*	*Abnormal number of points*	*Total abnormal records*
Aortic stenosis	14	11	11	8	3	3	14	14
Mixed aortic stenosis and aortic insufficiency	12	4	12	4	0	8	11	12
Mitral insufficiency	8	3	5	0	3	5	8	8
Aortic insufficiency	5	2	4	1	1	3	5	5
Systemic hypertension	7	1	7	1	0	6	7	7
Total	46	21 (46%)	39 (85%)	14 (30%)	7 (15%)	25 (54%)	45 (98%)	46

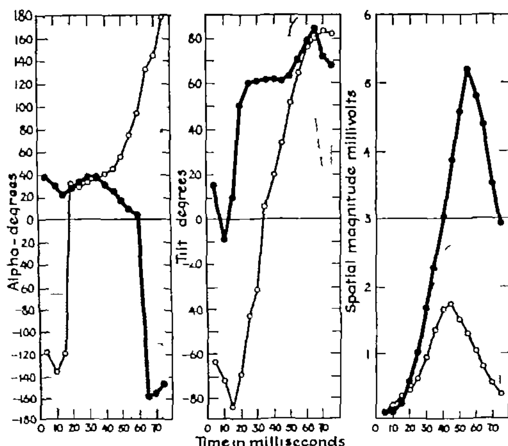


Fig 2 Each spherical coordinate of the calculated instantaneous heart vectors is graphed as a function of time. The shaded areas represent the scatter of ±2 standard deviations found among normal men from 30 to 40 years of age. The plot for a normal individual (○ — ○) and for a patient with severe aortic stenosis (● — ●) are shown.

msec the number of points above the group means in spatial magnitude and within the afore-mentioned divisions of standard deviation were tabulated. The extremes listed below were found among normal individuals.

In the tendency to tilt posteriorly in the first 40 msec (a) three normal subjects (2 per cent) had 1 point greater than 3 standard deviations from their group means (b) five normal subjects (3 per cent) had 3 or more points greater than 2 standard deviations from the means (c) eleven normal subjects (7 per cent) had 2 or more points greater than 2 standard deviations from their means. In the tendency for increased spatial magnitude from 35 to 75 msec. (a) no normal subjects had a point greater than 3 standard deviations above the means (b) seven normal subjects (4.5 per cent) had 3 or more points greater than 2 standard deviations above the means (c) thirteen normal subjects (8 per cent) had 2 or more points greater than 2 standard deviations above the means.

If the points falling in each division of standard deviations described above were weighted as follows, a value between 1.5 and 2 S.D = ½ point a value between 2 and 3 S.D = 1 point a value between 3 and 4 S.D = 2 points and a value greater than 4 S.D = 3 points, and if both abnormal tendencies were then considered together in each record the normal group showed the following extremes (a) three normal subjects (2 per cent) totaled 5 or more points (b) eight normal subjects (5 per cent) totaled 4 or more points and (c) fifteen normal subjects (10 per cent) totaled 3 or more points.

Both the sensitivity and specificity of

this method as a diagnostic test for left ventricular hypertrophy depends upon the values chosen as the upper limit of normal. If one decides to tolerate up to 5 per cent of normal individuals in the abnormal range, then the following three criteria indicate the presence of left ventricular hypertrophy

1 If during the first 40 msec. the heart vector is tilted posteriorly greater than 2 standard deviations from the mean in 3 or more instantaneous samplings, or

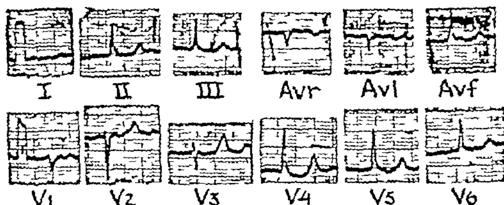


Fig 3 The plot for a 24-year-old woman with moderately severe mitral insufficiency is shown against the normal background of her age and sex group, demonstrating abnormal tilting of the vector forces posterior to normal in the early part of ventricular activation. Her 12-lead electrocardiogram taken the same day is shown.

Table II Comparison of results of the orthogonal 3-lead system with the standard electrocardiogram

Clinical group	Number of cases	Orthogonal leads		Standard ECG	
		LV abnormality	Normal	LVH	Normal
Aortic stenosis	14	14	0	13	1
Mixed aortic stenosis and aortic insufficiency	12	12	0	11	1
Aortic insufficiency	5	5	0	4	1
Mitral insufficiency	8	8	0	4	4
Systemic hypertension	7	7	0	5	2
Total	46	46	0	37	9

greater than 3 standard deviations from the mean in one or more samplings, left ventricular hypertrophy is present.

2 If within the period from 35 to 75 msec the heart vector is increased in spatial magnitude greater than 2 standard deviations from the mean during 3 or more instantaneous vectors or greater than 3 standard deviations from the mean during one or more samplings, left ventricular hypertrophy is present

3 With the use of the described point system of quantitation if a patient shows a total of 5 or more points toward the combined tendencies of posterior tilt and increased spatial magnitude then left ventricular hypertrophy is present.

The results of comparing the abnormal group with each of the foregoing three criteria are shown in Table I

Twelve-lead electrocardiograms taken at the time of the 3-lead records and interpreted by senior members of the Cardiology Department of this institution were available for all of the 46 patients with heart disease In order to compare the results of the two methods the conclusions drawn from the scalar electrocardiograms were tabulated into two categories (1) suggesting or indicating left ventricular hypertrophy and (2) normal or showing abnormalities not suggesting left ventricular hypertrophy

It should be noted that conclusions from the routine electrocardiograms included assessment of changes in the ST T wave as well as QRS activity whereas the interpretation of the 3-lead system has not yet been extended to include S-T-segment and T wave activity These findings are presented in Table II

Discussion

The instantaneous heart vector calculated from 3 orthogonal leads may be considered as the resultant of directed electrical forces generated from the cardiac septum free right ventricular and free left ventricular walls, as manifested on the body surface. The changes in direction and magnitude of the summation heart vector seen in the group of abnormal subjects in this study can be hypothetically attributed to an increase in electrical potentials produced in the myocardial mass of the left ventricular portion of the septum and the free left ventricular wall It was found that during the first 40 msec of activation the resultant heart vector tended to deviate as though an additional component directed toward the left posterior octants in space were added However during the latter part of ventricular activation the resultant sample vectors maintained a normal transition in direction but were increased in magnitude. This is the period in which the contribution of the free left ventricular wall is believed to dominate the electrical activity of the heart so that increases in potential from this region would be expected to cause little change in direction of the resultant heart vector even though they produce an increase in potential magnitude. These findings in vector terms

indicate the manner in which the time-varying electrical field generated by ventricular activation is altered by left ventricular overwork.

It is notable that the difference in result from the electrocardiogram demonstrated in this study depended in almost half of the instances upon the detection of less than normal anterior tilting of the electrical forces during the early part of ventricular activation. This generally corresponds in the clinical electrocardiogram to small amplitude r waves in the right precordial leads or to narrowed r waves, i e a reduced intrinsicoid deflection in these leads. Wilson[11] noted small r waves associated with left ventricular hypertrophy but Sokolow et[12] normal subjects and those with left ventricular hypertrophy showed too little difference in the measured height of the right precordial r waves or the intrinsicoid deflection to make them a criteria of left ventricular hypertrophy This is unfortunate for of the 9 patients in the present group who had normal electrocardiograms, 4 showed only this evidence of left ventricular overwork. Fig 3 demonstrates this in a patient who had moderately severe mitral insufficiency However these patients were not confined to any one clinical condition

In 2 cases the 12-lead electrocardiogram failed to show diagnostic voltage magnitudes in the precordial leads because the mean electrical axis was such that its null plane fell along the alignment of the precordial electrodes and thus produced normal voltage Rs complexes in left precordial leads that is to say the mean electrical axis was perpendicular to the recording axes of the precordial leads. In this situation it may be an advantage to detect abnormal increases in voltage by the derived heart vector for the magnitude of such a quantity is independent of the orientation of the reference axes to the electrical field of the heart The derived heart vector magnitude was markedly abnormal in each of these cases.

The comparison made between the results of this method and the serial electrocardiograms suggests an increased sensitivity to abnormality of the method used in this investigation However the criteria of abnormality used were defined according to what the present group of abnormal subjects demonstrated therefore, an unbiased comparison will require another series of patients with heart disease causing isolated left ventricular overwork.

It also remains for future studies to determine how specific these described deviations from normal are for left ventricular overwork and hypertrophy for there may well be overlap with other myocardial abnormalities which affect ventricular activation

Summary

From the records of the orthogonal 3-lead system of Helm the polar coordinates of the time varying spatial heart vector of ventricular activation were calculated. Forty-six patients with clinical conditions which caused isolated left ventricular overwork were compared with 154 normal control subjects. Variation from normal in the group of patients with left ventricular overwork could be divided into two categories less than normal anterior tilting of the heart vector during the first 40 msec of ventricular activation and an increase in the spatial magnitude of the heart vector from 35 msec. to the end of ventricular activation. The results of the study represent the changes in the vector forces derived from the body surface during ventricular activation which occur in isolated overwork of the left ventricle. The difference in result between the orthogonal 3 lead system and the serial 12 lead electrocardiogram appeared to be dependent mostly on the detection of abnormal direction of the heart vector along an antero-posterior body axis for short periods during the initial half of ventricular activation.

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REFERENCES

1 Schmitt, O and Simonson, E. The present status of vectorcardiography A.M A. Arch Int. Med 96:574 1955
2. Burger H. Lead vector projections J Am. New York Acad. Sc 65 1076, 1957
3. Frank, E. An accurate, clinically practical system for spatial vectorcardiography Circulation 13 737 1956.
4 Helm R. An accurate lead system for spatial

vectorcardiography Am. Heart J 53:415 1957
5. McFee R. and Parungao, A. An orthogonal lead system for clinical electrocardiography Am. Heart J 62:93, 1961
6. Pipberger H Bealek, S., Perloff J and Schnaper H Correlation of clinical information in the standard 12 lead ECG and in a corrected orthogonal 3-lead ECG Am. Heart J 61:34, 1961
7. Groeben, J von der A comprehensive mapping of spatial vectorcardiographic data Am. Heart J 56:510 1958.
8. Forsythe G., Groeben, J von der and Toole, J: Vectorcardiographic diagnosis with the aid of ALGOL, Applied Mathematics & Statistics Laboratory Technical Report No. 16, Contract No. nr 225(37) Stanford University 1961
9. Grant, R. Clinical electrocardiography New York, 1957 McGraw Hill Book Company Inc.
10. Groeben, J von der The spatial frequency distribution of the QRS loop as studied on 154 normal individuals, Am Heart J 59:875 1960
11. Wilson F Johnston, F., Rosenbaum, F., Erlanger H Kossmann, C., Hecht, H Cotrim, M de Oliveira R. Scarsi R., and Barker P The precordial electrocardiogram Am. Heart J 27:19 1944
12. Sokolow M and Lyon, T The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads, Am Heart J 37:161 1949

The prevention of tissue necrosis with a levarterenol-adrenolytic mixture

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The use of levarterenol (*l* norepinephrine Levophed) in combating shock due to various causes is of proved value A major disadvantage which accompanies the use of this drug has been the development of ischemic necrosis in areas of accidental extravasation It has been demonstrated clinically that adrenolytic drugs (phentolamine and piperoxan) infiltrated at the area of extravasation can prevent the development of necrosis and tissue slough[1-4] Recently Zucker and Levine have reported the successful administration of levarterenol-phentolamine mixtures as a prophylactic measure in the prevention of possible necrosis after extravasation

The present study was undertaken to find an adrenolytic capable of preventing local tissue necrosis after levarterenol extravasation which was stable in solution possessed a high order of adrenolytic activity and was compatible with the clinically useful systemic pharmacodynamic properties of levarterenol. Such a compound might also permit intramuscular and subcutaneous administration of levarterenol during emergency situations.

The compound chosen designated solypertine is an indolyl phenylpiperazine which possesses a high order of adrenolytic activity It was synthesized by Archer and co-workers[5] and has the chemical name 1 (2-anisyl)-4- 2-{3-(5 6 methylenedioxy indolyl) }-ethyl piperazine Studies have been conducted on the base and tartrate salt because the latter is more soluble it is currently being used in clinical studies. The adrenolytic activity of solypertine as determined by its ability to protect rats against lethal effects of norepinephrine using the technique of Luduena and co-workers,[6] was high The ED_{50} value was 11 8 ± 5 3 microgram base per kilogram[7] compared to 14 8 microgram base per kilogram for phentolamine and 240 microgram base per kilogram for piperoxan[8] Solypertine produces a depressant effect on the central nervous system but at relatively high dose levels compared to those at which it has effective adrenolytic action[4]

Methods

The infiltration of the subcutaneous tissue of the experimental animal with levarterenol solution is the only practical way of producing consistent tissue damage The concentration of levarterenol is not so important as the duration of the vasoconstriction [2] Consequently slow infusion over a relatively long period with clinical dilutions of levarterenol is important and necessary

Studies of tissue damage were conducted with the rabbit. The animals were placed supine on a rabbit board and the abdominal area was carefully shaved with clippers.

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They were sedated with morphine 10 mg per kilogram subcutaneously Thirty minutes later subcutaneous infusion into the abdominal tissue was begun using a gravity flow pressure system connected to a 1.5-inch No 22 hypodermic needle. The flow was regulated to produce an infiltration of 1 ml per minute Isotonic saline was used as the control and commercial levarterenol (Levophed) diluted in isotonic saline at a concentration of 4 microgram base per milliliter was used to produce tissue pathology At the completion of the period of infusion the boundary of the abdominal surface area involved was marked and measured It was observed at regular intervals during the succeeding 3 to 5 days at the end of this period the animals were sacrificed autopsied and classified as to the degree of tissue damage.

The experimental procedure used to examine the adrenolytic levarterenol combinations was identical to that used in the control studies with the addition of the adrenolytic to the infusion solutions Comparative studies were conducted with phentolamine. Various dosages of levarterenol and solypertine were studied in an effort to ascertain the most effective ratio in preventing tissue damage

Systemic pressor and cardiac studies were conducted in dogs anesthetized with pentobarbital 30 mg per kilogram intravenously and artificially respired on room air The animals were prepared for oscillographic measurement of arterial blood pressure (Statham transducer) heart contractile force (Walton strain gauge) and heart rate and recording of the electrocardiogram (Lead II) The adrenolytic (solypertine) was administered intravenously at hourly intervals in successive doses of 0 25 0 5 and 1 0 mg per kilogram to 5 dogs and at hourly intervals in successive doses of 2 0 4 0 and 8.0 mg per kilogram to a second group of 5 dogs. Each dog was challenged with a single intravenous injection of levarterenol 0.5 microgram per kilogram 15 30 45 and 60 minutes after each injection of the adrenolytic. These responses were compared to control values obtained for levarterenol prior to the first injection of the adrenolytic.

A second series of experiments were conducted in dogs to evaluate the reversal and inhibitory activity of solypertine on levarterenol isoproterenol and epinephrine. Six dogs were prepared as outlined above for measurement of arterial blood pressure heart contractile force heart rate and recording of the electrocardiogram. Control values were obtained for each amine The adrenolytic solypertine was then administered at a dose of 100 micrograms per kilogram intravenously after which the animal was challenged intravenously with each amine at intervals of 0 5 1 2 and 3 hours. Levarterenol was administered at a dose of 0 5 microgram base per kilogram *l*-epinephrine at 0.5 microgram base per kilogram and *l* isoproterenol at 0 1 microgram base per kilogram

Intramuscular and subcutaneous activity of the levarterenol-adrenolytic mixture was examined in a series of 14 dog experiments The animals were prepared as outlined above for measurement of cardiovascular activity The levarterenol adrenolytic mixture used was a 2 1 ratio which contained 4 0 mg of levarterenol base and 2 0 mg of solypertine base in 4 0 ml solution This concentrated solution was administered at random sites in the thigh and foreleg for intramuscular injections and at random sites in the abdomen and flank for subcutaneous injection No two injections were administered into the same area of tissue Seven animals which served as their own controls were given one or more injections of levarterenol alone at the same dose levels (micrograms per kilogram) as levarterenol in the mixture.*

Results

The results of tissue pathology due to infusion experiments with control saline and levarterenol are tabulated in Table I These experiments show that 200 ml of levarterenol solution (4 micrograms per milliliter) infused into the subcutaneous tissue of the rabbit abdomen consistently produces tissue damage similar in nature to the clinically observed tissue slough after extravasation of levarterenol Smaller vol

*Acute toxicity data for solypertine were kindly supplied by Dr J O Hoppe These data were obtained using mice for intravenous and subcutaneous toxicity using standard techniques to determine LD_{50} values.

Table I Tissue pathology in rabbits after subcutaneous infusion of saline and levarterenol

Solution and dose	*Volume† of infusion (ml.)*	*Number of animal*	*Gross tissue pathology*—Number of animal*				*Average score*
			Grade 1	*Grade 2*	*Grade 3*	*Grade 4*	
Control (isotonic saline)	200	8	8	0	0	0	1.0
Levarterenol	50	8	4	0	0	4	2.5
(4 micrograms	100	8	4	0	0	4	2.5
per milliliter of	150	8	3	1	0	4	2.5
isotonic saline)	200	8	0	0	1	7	3.9

*See Table II and text for explanation of grading of gross tissue pathology.
†Rate of infusion was 1 ml. per minute in all experiments.

times and doses, given in a shorter absolute time do not produce the same consistent degree of tissue change. Isotonic saline given in the same total fluid volume and of the same infusion duration did not produce tissue ischemia or other pathologic changes.

The grading scale used to measure the degree and extent of tissue pathology is outlined in Table II. Two hundred milliliters of infused fluid produced an edematous area of subcutaneous tissue which was approximately 18 by 16 cm. in dimension. The epithelial surface was raised approximately 1 cm. at the center of the involved tissue. Within 24 hours the edematous area was reduced by 50 per cent and had usually completely disappeared within 48 hours. In animals which received the control solution of isotonic saline the epithelial surface of the edematous area was pink and warm to the touch at 24 hours and similar in appearance to normal uninvolved adjacent tissue. In those animals which received levarterenol the area involved was blanched and cool to the touch which indicated vasoconstriction and reduced blood flow. In those animals which received levarterenol and the adrenolytic (solypertine) the appearance of the infused area was similar to that of animals which received isotonic saline.

The development of epithelial and subcutaneous lesions was progressive. The first signs of an impending lesion appeared at 24 hours after the infusion and followed the disappearance of the blanching. The lesion is characterized by a large central mottled area, pale purple and white and surrounded by a circle of bright pink tissue. The central coloring is produced by a bloody edematous exudate located in the underlying subcutaneous tissue. The epithelial surface is moist to the touch and the size of the central involvement is one fourth to one third of the original large blanched edematous tissue mass of the immediate postinfusion period. By 48 hours the area involved is further reduced in size and more clearly defined. It is oval in shape and approximately 4 by 5 cm. in outline although there tends to be some variation in size. The mottled color now changes to a solid purple area with a blanched peripheral halo. The circle of bright pink tissue disappears and

Table II Gross pathology descriptive grading

Grade number	*Tissue damage*
1	No damage to epithelial or subcutaneous tissue
2	Epithelial tissue—Normal Subcutaneous tissue—Small nodular adhesions
3	Epithelial tissue—Normal Subcutaneous tissue—Larger adhesions and small necrotic areas
4	Epithelial tissue—Overtly necrotic Subcutaneous tissue—Excessive adhesions and necrosis area involved greater than epithelial surface in [illegible]

Table III Studies of tissue pathology and protection in rabbits treated with levarterenol and solypertine

Solution and dose	Drug ratio	Volume infused (ml.)	Number of animals	Gross tissue pathology—Number of animals				Average score
				Grade 1	Grade 2	Grade 3	Grade 4	
Levarterenol 4 γ/ml. Solypertine 0.5 γ/ml.	8:1	200	12	0	0	0	12	4.0
Levarterenol 4 γ/ml. Solypertine 1 γ/ml.	4:1	200	15	6	2	5	2	2.2
Levarterenol 4 γ/ml. Solypertine 2 γ/ml.	2:1	200	55	47	3	4	1	1.25
Levarterenol 4 γ/ml. Phentolamine 2 γ/ml.	2:1	200	25	12	0	12	1	2.1

a scab-like surface begins to develop. If the area is allowed to heal naturally and no secondary infection occurs, the overt necrosis gradually disappears in approximately 2 weeks and is replaced by scar tissue. The epithelial surface scar is smaller than the underlying subcutaneous scar with its permanent multiple adhesions.

Not all lesions develop the extreme pathologic picture. In a moderate number of lesions the epithelial surface is apparently normal, however, the underlying subcutaneous tissue may or may not develop pathology. When pathology does occur, the degree of damage is variable, as indicated by the Grades 2 and 3 classification in Table II. These less severe lesions usually appear in those instances in which the adrenolytic has been used. It would appear that the adrenolytic has, in these instances, offered partial protection from the necrotizing action of extreme levarterenol vasoconstriction.

The results of infiltration of tissue by various combinations of levarterenol and solypertine are outlined in Table III. The combination ratio of 2:1 (levarterenol to adrenolytic) offered the most satisfactory protection. Our experiments also demonstrate that solypertine offered better protection from levarterenol than did phentolamine at the dose levels examined. There is considerable reduction in protection with the 4:1 ratio and no protection with the 8:1 ratio.

The cardiovascular activity of solypertine as it interferes with and inhibits the pressor and inotropic actions of levarterenol have been summarized in Table IV. The maximum depression and inhibition of the levarterenol response by solypertine occurs 30 to 45 minutes after the administration of the adrenolytic. With successive doses of solypertine the cumulative effect on further injections of levarterenol is increased. However, cumulative doses to 14 mg. per kilogram base of solypertine reduce the pressor response to levarterenol by approximately 25 per cent, whereas the inotropic activity of levarterenol is reduced by approximately 75 per cent. This suggests a high probability that solypertine will not interfere with or reduce the therapeutic effect of levarterenol at the anticipated clinical dose levels.

The second series of amine experiments which relate the reversal or depressant actions of solypertine on epinephrine, levarterenol, and isoproterenol have been summarized in Table V. These studies show that solypertine given as a single dose of 100 microgram base per kilogram intravenously will produce a significant reversal of epinephrine pressor activity. Maximum reversal of epinephrine occurred 30 minutes after administration of solypertine, and during the succeeding 2.5 hours it continued to produce reversal although to a somewhat lesser degree. The duration of the epinephrine reversal was

Table IV Cardiovascular responses to intravenous levarterenol in dogs treated with cumulative doses of solypertine, an adrenolytic

Drug	Dose (mg./Kg.)	Number of dogs	Cumulative dose (mg./Kg. I.V.)	Mean change after levarterenol challenge (0.5 γ/Kg. I.V.)*				
				Blood pressure		Heart contractile force		
				Increase in mean pressure (mm. Hg)	Increase in diastolic pressure (mm. Hg)	Amplitude (mm.) excursion: Control	Amplitude (mm.) excursion: Experimental	Per cent increase
Levarterenol	0.5 microgm.	10	——	35.1	26	11.4	19.5	71.0
Solypertine	Series I	5						
	0.25		0.25	39.6	24	10.5	18.4	75.2
	0.50		0.75	26.2	22	11.8	18.5	56.7
	1.00		1.75	28.5	24	13.1	18.6	42.0
	Series II	5						
	2.0		2.0	30.2	25	11.8	16.9	43.2
	4.0		6.0	24.4	20	12.0	16.1	34.1
	8.0		14.0	23.4	19	11.5	14.3	24.3

*Values obtained from challenge 45 minutes after adrenolytic.

*Table V Amine cardiovascular changes subsequent to administration of solypertine**

Drug	Dose (mcg./Kg. I.V.)	Time (hours)	Per cent change: Heart contractile force	Per cent change: Mean blood pressure	Heart rate
l-Epinephrine	0.5	Control	+94.5	+19.0	+7.8
Solypertine	100	—	—	—	—
l-Epinephrine	0.5	0.5	+99.1	−34.5	+6.5
	0.5	1.0	+92.3	−28.7	+4.9
	0.5	2.0	+97.0	−26.1	+8.6
	0.5	3.0	+91.5	−23.3	+6.8
l-Norepinephrine	0.5	Control	+87.0	+61.1	+1.9
Solypertine	100	—	—	—	—
l-Norepinephrine	0.5	0.5	+95.5	+48.5	−9.7
	0.5	1.0	+89.9	+42.1	−1.5
	0.5	2.0	+96.7	+41.5	+0.9
	0.5	3.0	+83.8	+42.6	+2.9
l-Isoproterenol	0.1	Control	+118.0	−46.5	+35.8
Solypertine	100	—	—	—	—
l-Isoproterenol	0.1	0.5	+133.8	−45.8	+30.1
	0.1	1.0	+1 7.1	−43.3	+30.1
	0.1	2.0	+135.0	−44.1	+33.6
	0.1	3.0	+119.7	−45.3	+24.5

*Six animals were used in these experiments. Each animal received each amine at the times specified. Although solypertine was administered only once, the data have been rearranged to facilitate comparison between amines and time intervals.

Table VI Cardiovascular responses after intramuscular and subcutaneous administration of levarterenol-solypertine combination and levarterenol

Drug + Dose (microgram/Kg)	*Route of administration*	*Number of animals**	*Per cent increase in mean blood pressure*	*Per cent increase in contractile force*	*Time (min)*		
					Onset	*Peak*	*Duration*
Levarterenol—20 Solypertine—10	Intramuscular	2(2)	151.3	75.0	16	23	68
Levarterenol—10 Solypertine—5	Intramuscula	8(8)	46.6	96.8	12	22	59
Levarterenol—5 Solypertine—2.5	Intramuscular	4(2)	9.0	27.8	8	21	53
Levarterenol—10	Intramuscular	4(0)	0	0	—	—	—
Levarterenol—5	Intramuscular	3(0)	0	0		—	—
Levarterenol—40 Solypertine—20	Subcutaneous	5(3)	8.2	23.8	25	36	77
Levarterenol—20 Solypertine—10	Subcutaneous	5(4)	42.4	61.0	21	29	75
Levarterenol—10 Solypertine—5	Subcutaneous	5(1)	9.0	10.0	34	37	70

*Number of animals used for administration of each drug, with the number of animals exhibiting an effective drug response indicated in parentheses.

greater than 5 hours. There was little reduction of the epinephrine inotropic or chronotropic activity. Solypertine at a single 100 microgram per kilogram dose had little effect on the pressor and inotropic activity of levarterenol and little effect on the depressor and inotropic activity of isoproterenol.

Studies to evaluate the cardiovascular activity of the levarterenol-adrenolytic mixture after intramuscular and subcutaneous administration carried out in dogs prepared for oscillographic recording of the standard cardiovascular parameters are summarized in Table VI. The levarterenol-solypertine mixture was effective in producing a cardiovascular response when administered intramuscularly; this response was related to the dose and was more effective and reproducible than that due to subcutaneous administration. This fact may be accounted for by the greater degree of vascularity of muscle as compared to subcutaneous tissue. In no instance were we able to demonstrate a systemic blood pressure or inotropic response after injections of levarterenol alone. The responses obtained after intramuscular injection of the mixture at doses of 10 and 5 micrograms per kilogram of levarterenol and solypertine, respectively, produced consistent good increases in blood pressure and cardiac contractile force; time of onset, peak response, and duration of action were essentially equal to those responses obtained with twice this dose, i.e., 20 and 10 micrograms per kilogram of levarterenol and solypertine, respectively. Halving the 10:5 dose did not always produce a cardiovascular response.

Comparative toxicity data for solypertine, phentolamine, and piperoxan are presented in Table VII. We have included adrenolytic activity, intravenous and subcutaneous toxicity, and intradermal irritancy for each compound as well as relative values between compounds.

Discussion

Levarterenol is the most active pressor amine used clinically to overcome extreme hypotensive states. As a result of its potent vasoconstrictor activity, it may, under adverse conditions and after accidental extravasation, produce tissue damage and necrosis. This has been well documented in the existing literature. Other drugs which possess similar pharmacologic profiles but a lower degree of relative potency have not been reported to produce tissue damage after extravasation with the same

frequency as levarterenol. Consequently other amines have been used with increasing frequency but with this increased use, cases of tissue necrosis after extravasation have recently been reported.[3,4] The answer may well be in the different intrinsic activities as well as the relative potencies of those amines currently used. There can be no doubt that less active amines with their lower relative potencies and less marked vasoconstrictor activity are less likely to produce tissue damage after accidental extravasation than is a more active amine. Nevertheless, these less active amines do produce tissue damage and the point to be emphasized is that any active vasoconstrictor given in a large enough dose in sites of reduced blood flow may produce tissue damage after accidental extravasation. Another point to be emphasized is obvious but often overlooked, that is, the need for adequate nursing care and careful observation of the seriously ill patient to whom these active, often lifesaving vasopressor drugs are essential.

The present studies demonstrate that a new adrenolytic solypertine when combined with levarterenol can prevent tissue necrosis after infiltration of the subcutaneous tissue. Not only is tissue damage prevented but when levarterenol is combined with solypertine it produces a sustained moderate cardiovascular response after intramuscular administration. Whatever the mechanism of protection by the adrenolytic it appears to prevent the intense local vasoconstriction of levarterenol at dose levels that do not alter the systemic responses to levarterenol. It may be that because of the relatively large molecular size solypertine does not diffuse from the subcutaneous tissue so rapidly as levarterenol. By the same token after intramuscular administration solypertine counteracts the intense limiting vasoconstriction of levarterenol and permits levarterenol to move slowly from the site of administration into the systemic circulation.

Studies by Luduena and associates[6] suggest that the protective action exhibited by adrenolytics in preventing epinephrine or norepinephrine toxicity was the result of peripheral antagonism of the vasoconstrictor action. The intense sustained high arterial blood pressure with concomitant increased force of myocardial contraction could account for the occurrence of pulmonary edema after epinephrine and norepinephrine toxicity. It is suggested that the adrenolytic drugs probably act by partial blockade of the adrenergic receptor site and thus reduce

Table VII. Adrenolytic activity, toxicity, and irritancy of solypertine, phentolamine, and piperoxan

Compound	*Adrenolytic activity in rats*		*Intravenous toxicity in mice*		*Subcutaneous toxicity in mice*		*Intradermal irritancy (trypan blue test)*	
	ED_{50} (mg/Kg)	*Relative activity of piperoxan = 1*	$LD_{50} \pm$ S.E. (mg/Kg)	*Relative toxicity of piperoxan = 1*	$LD_{50} \pm$ S.E. (mg/Kg)	*Relative toxicity of piperoxan = 1*	TIC_4 (%)	*Relative irritancy of piperoxan = 1*
Piperoxan (Benodaine HCl)	240	1	26.3 ± 1.8	1	1040 ± 103	1	1.0	1
Phentolamine (Regitine HCl)	14.8	16	61.5 ± 4.3	0.42	—	—	0.25	4
Solypertine (a tartrate salt)	12	20	31.0 ± 2.0	0.85	158 ± 13	6.5	0.125	8

*Values in terms of the base. The LD_{50} and TIC_4 values are in terms of the salts, as indicated.

the degree and duration of the rise in arterial pressure effected by levarterenol. The evidence suggests that the adrenolytic drugs alter the dose-response curves for epinephrine and levarterenol probably by changing the slope of these curves.

Two recent studies[11,12] have suggested that the classic adrenergic blocking drugs of the *alpha* type (Ahlquist classification) do not specifically block the positive inotropic activity of levarterenol, epinephrine, or isoproterenol. Blockade, when it does occur, is of nonspecific nature compared to the specific *beta* blockade of dichloroisoproterenol. We have examined our studies in the light of these recent reports by Nickerson and Chan[11] and Moran and Perkins,[12] and find that solypertine apparently does specifically block the inotropic activity of levarterenol while producing minimal inhibition of the pressor activity. This we interpret to mean that solypertine produces more effective blockade of the *beta* adrenergic receptor than of the *alpha* receptor. These studies are continuing and will be the subject of a separate publication.

Summary

1. Solypertine, 1-(2-anisyl)-4-[2-[3-(5,6-methylenedioxyindolyl)]-ethyl]-piperazine, possesses a high degree of adrenolytic activity that is comparable to that of phentolamine.

2. Experimental studies in rabbits demonstrate that solypertine protects against levarterenol-induced tissue damage. The optimal ratio appears to be 2:1 (4 micrograms of levarterenol and 2 micrograms of solypertine base per milliliter). This ratio afforded the least tissue damage with the lowest relative possible concentration of the adrenolytic.

3. Tissue protection after levarterenol-solypertine (2:1 ratio) was superior to that after levarterenol-phentolamine (2:1 ratio).

4. Cardiovascular studies in dogs suggest that solypertine used at the optimal ratios will not interfere with the systemic cardiovascular activity of levarterenol.

5. It appears that levarterenol-solypertine mixtures used at the 2:1 ratio will permit the use of levarterenol by intramuscular and subcutaneous injection as well as by the established procedure of intravenous infusion.

The authors wish to express grateful acknowledgment to Dr. J. O. Hoppe for the acute toxicity and irritation experiments on solypertine, piperoxan, and phentolamine. We also wish to express our gratitude to Dr. H. P. Drobeck and Dr. D. J. Sullivan for their able guidance with the tissue pathology portions of this study.

REFERENCES

1. McGinn, J. T., and Schluger, J.: Skin sloughs associated with Levophed: pathogenesis, prevention and treatment, Am. J. Surg. 92:594, 1956.
2. Zucker, G., and Eisinger, R. P.: Prevention of levarterenol necrosis in rabbits by use of levarterenol-phentolamine mixtures, Proc. Soc. Exper. Biol. & Med. 103:260, 1960.
3. Pelner, L.: Treatment of local ischemia due to levarterenol leakage with piperoxan, J.A.M.A. 165:444, 1957.
4. Zucker, G., and Levine, J.: Pressor and diminished local vasoconstrictor effects of levarterenol-phentolamine mixtures, A.M.A. Arch. Int. Med. 104:607, 1959.
5. Archer, S., et al.: To be published.
6. Luduena, F. P., O'Malley, E., and Oyen, I. H.: Effect of adrenergic blockers and related compounds on the toxicity of epinephrine in rats, Arch. internat. pharmacodyn. 122:111, 1959.
7. Wylie, D. W., and Archer, S.: To be published.
8. Harris, L. S.: Unpublished data.
9. Dippy, W. E., and Dorney, E. R.: Tissue necrosis and slough produced by metaraminol bitartrate, J.A.M.A. 170:1647, 1959.
10. Shaub, R.: Ischemic necrosis due to administration of metaraminol, J.A.M.A. 172:154, 1960.
11. Nickerson, M., and Chan, G. C. M.: Blockade of responses of isolated myocardium to epinephrine, J. Pharmacol. & Exper. Therap. 133:186, 1961.
12. Moran, N. C., and Perkins, M. E.: Evaluation of adrenergic blockade of mammalian heart, J. Pharmacol. & Exper. Therap. 133:192, 1961.

Flow patterns in the heart and great vessels of man
Preliminary report on the radiopaque streamer technique

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Currently available techniques for the clinical study of the heart and circulation do not provide detailed information about the instantaneous flow patterns in the heart and great vessels throughout the cardiac cycle. Recently Doby[1,2] reported the insertion of radiopaque streamers into the hearts of experimental animals and demonstrated the motion of these streamers with cineradiographic techniques. It appeared that this approach could prove to be useful in the determination of the motion of blood within the heart and great vessels in normal and abnormal states and that such studies could provide useful information in regard to cardiac dynamics.

Methods

The streamers used are modifications of those described by Doby and consist of a 2.5 to 3.0 cm length of "00" silk suture attached to the end of a number 7 "bird's eye" catheter (Fig 1). The radiopaque bead at the end of the streamer is fashioned by immersing the frayed end of the suture into a semiliquid mixture of pure white lead and linseed oil. The streamer is then baked in an oven at 90°C. until it hardens. The processes of immersion and baking are repeated until a lead bead of the desired size is obtained. A bead that is 2.0 mm in diameter has been found to be satisfactory for use in most adults. Streamers with beads of 1.0 and 1.5 mm diameter are utilized for children or small adults. When the beads are of the desired size, they are coated with a thin layer of liquid Lucite.* After this dries, the streamer is attached to the end of the bird's eye catheter by passing the suture material into the end hole out one of the side holes and then tying it securely. The small knots are placed over the end hole of the catheter so that they do not protrude beyond its width. The knots are then covered with the liquid Lucite which serves to secure the knot as well as to maintain its position in relation to the tip of the catheter. Any rough edges of Lucite are smoothed with a file. The streamer is then dipped into an undiluted solution of Siliclad† a physiologically inert substance designed to prevent the formation of blood clot.[3] The catheter streamer combination is sterilized

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*Lucite dissolved in chloroform.
†Clay-Adams, Inc., New York, N.Y.

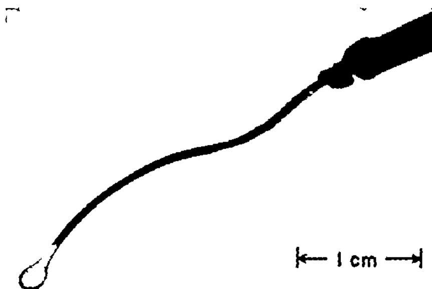


Fig. 1. The streamer: a white lead bead on "00" silk suture attached to the end of a number 7 "bird's eye" catheter.

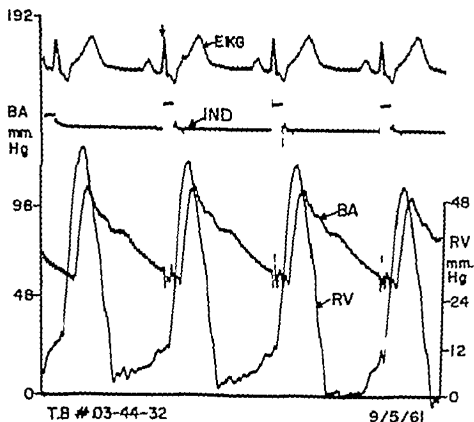


Fig. 2. Observations recorded simultaneously with the cineradiogram. *EKG*: Electrocardiogram. *IND*: Timing of R-wave indicator. *BA*: Brachial arterial pressure. *RV*: Right ventricular pressure.



Fig. 3 A cineradiographic frame which shows the position of the radiopaque bead during ventricular systole with the tip of the catheter in the right ventricle. The R-wave indicator is seen adjacent to the right heart border.

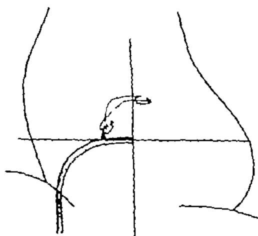


Fig. 4 Motion of the bead in the right ventricle during a complete cardiac cycle in a patient with pulmonic valvular regurgitation.

by means of ethylene oxide gas. Standard autoclaving methods are unsatisfactory because they melt the Lucite and the bead.

The catheter with streamer attached is introduced into a surgically exposed peripheral vein. The insertion of the streamer into the major vessels and the cardiac chambers is observed with an x-ray image intensifier. Cineradiographic film is then exposed at 30 frames per second. The electrocardiogram, the pressure in the chamber or vessel in which the tip of the catheter is located, and the systemic arterial pressure are recorded simultaneously with the cine exposures. A metallic indicator triggered by the R wave of the electrocardiogram is projected onto the cineradiographic image, and its motion is also recorded along with the hemodynamic data on a multichannel oscilloscopic recorder (Fig. 2).

In order to analyze the motion of the bead the cineradiographic image is projected onto a rectangular coordinate system. The tip of the catheter is placed at the origin of the coordinate system and the position of the bead in relation to the tip of the catheter is plotted for each individual frame for several cardiac cycles, utilizing the R wave indicator as the time reference point. The cardiac silhouette which exists at the instant of the electrocardiographic R wave is then superimposed on the coordinate system.

Results and discussion

After the feasibility and safety of the technique was demonstrated in dogs, observations were carried out in the systemic venous bed and the right side of the heart in 16 patients, and no complications have resulted. Analyses of flow patterns in the superior and inferior venae cavae, right atrium, right ventricle, and pulmonary artery have been carried out. In three instances the streamer was placed into the left atrium through an atrial septal defect.

Fig. 2 shows an example of the electrocardiogram and right ventricular and brachial arterial pressure pulses in a 7 year

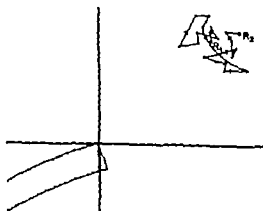


Fig. 5 Enlarged diagram which shows the motion of the bead in the right ventricle during a complete cardiac cycle in a patient with a normal pulmonic valve.

old boy studied 5 months after he had undergone valvulotomy for valvular pulmonic stenosis. At the time of this study the presence of pulmonary valvular regurgitation was clearly evident on an indicator dilution curve sampled from the right ventricle after injection had been made into the pulmonary artery.[4] The streamer was located in the right ventricle at the time of this recording. Fig. 3 illustrates the appearance of a cineradiographic frame and shows the radiopaque bead to be clearly visible. The movement of the radiopaque bead during the second cardiac cycle shown in Fig. 2 is plotted in Fig. 4. It is evident that during ventricular systole the bead was moved toward the pulmonic valve and that during diastole it was moved inferiorly and to the right. Fig. 5 demonstrates the motion of the bead in the right ventricle during a complete cardiac cycle in a patient with a normal pulmonic valve. In this case it is seen that the bead is directed toward the pulmonic valve throughout the cardiac cycle. Analysis of the data obtained from the patients studied suggests that the technique described may be especially useful in the diagnosis of valvular regurgitation. Other potential applications include the determination of the size and location of septal defects and the drainage sites of anomalous pulmonary veins.

In several instances it has been possible to place the streamer onto the surface of the tricuspid or pulmonic valve. In this manner it may become possible to analyze valve motion and to correlate this with simultaneously recorded hemodynamic and phonocardiographic data. The radiopaque streamer technique may prove to be helpful in determining the location of pulmonic and/or aortic orifices through which a standard cardiac catheter cannot be manipulated. We also plan to attempt to determine under what conditions turbulent blood flow occurs in the central circulation.

The possible complications which might have arisen as a result of the procedure, e.g., the detachment of the bead while in the heart, or the entanglement of the streamer around chordae tendineae were not encountered in the experimental animals nor in the 16 human subjects studied. With the method of manufacture of the beaded catheter described, it has been found that the forces necessary to remove the lead bead from the suture material are of considerable magnitude, which suggests that the possibility of such an occurrence is unlikely. The length of the suture material is purposely never made longer than 3.0 cm. so as to decrease the possibility of knotting around chordae tendineae.

Summary

The radiopaque streamer technique was utilized in the analysis of flow patterns within the heart and great vessels of 16 patients. Preliminary data suggest that the procedure may have valuable clinical application in the diagnosis of valvular regurgitation, in the determination of the size and location of septal defects, in locating the drainage sites of anomalous pulmonary veins, and in the study of valve motion.

REFERENCES

1. Doby, T., and Lowman, R. M.: Demonstration of blood currents with radiopaque streamer, Acta radiol. 55:272, 1961.
2. Doby, T.: Use of radiopaque streamers to show blood currents in heart, Radiol. 76:963, 1961.
3. Barondes, R. de R., Judge, W. C., Towne, C. G., and Metts, L. B.: The silicones in medicine, Mil. Surgeon 106:15, 1950.
4. Collins, N. P., Braunwald, E., and Morrow, A. G.: Detection of pulmonic and tricuspid valvular regurgitation by means of indicator solutions, Circulation 20:561, 1959.

Case reports

Calcified aneurysm of the left ventricular apex associated with intraventricular block of the left bundle branch type

A case report

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Deposition of calcium in the wall of an aneurysm of the left ventricle may proceed to a degree which permits reasonably precise delineation of the amount and location of scarring from myocardial infarction in a surviving patient. A clinicomorphologic-electrocardiographic correlation so derived is reported here.

Case report

A white man, 58 years of age, sought medical attention because of symptoms of fatigue and of periodic shortness of breath. His respiratory disorder was observed to be of a sighing type. Dyspnea and orthopnea were not present and the patient stated that he could walk a mile and one half without shortness of breath.

In 1944 he had received care in a hospital for a heart attack. He denied having had symptoms of angina pectoris either before or after that attack.

Review of the patient's records for the earlier hospitalization† disclosed that he was admitted to the hospital on Aug. 11 1944, because of severe pain in the chest which was accompanied by a sense of shortness of breath. Cardiac rate was 110 to 120 beats per minute. A gallop rhythm was heard. The attending physician entered the following description of the electrocardiogram: "The T waves in Lead I are flat and in Lead IV are completely changed and pathological (high up and not going back to zero line)." An unequivocal diagnosis of acute myocardial infarction was made.

Physical examination on June 5 1961, disclosed no substantial evidence of congestive cardiac failure. Systolic blood pressure ranged from 120 to 134 mm. Hg, and the diastolic pressure ranged from 80 to 90 mm. Hg. The ventricular rate was 90 beats per minute, and the heart was enlarged.

Review of the posterior-anterior roentgenogram of the chest (Fig. 1) disclosed that the cardiac silhouette was at the upper limits of normal in size. A hemispheric shell of calcific material, 2 to 7 mm. in thickness, formed the apex of the left and the inferior margins of the cardiac shadow. The terminal segment of each limb of the hemisphere deviated from the border of the cardiac silhouette into the substance of that shadow. The right anterior oblique thoracic roentgenogram (Fig. 1) placed this calcific segment of the cardiac shadow in sharper relief. It encompassed a localized protrusion of ventricular wall beyond the usual contour of the cardiac silhouette. On fluoroscopic examination, the calcific area of myocardium was said to move in concord with left ventricular pulsations.

An electrocardiogram made on May 22, 1961, is reproduced in Fig. 2. Noteworthy are the changes in the ventricular complexes. Existence of intraventricular block is documented by a QRS interval of 0.16 second in complexes of sinus origin. In all standard limb and unipolar extremity leads, and in

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Precordial Leads V1 and V2, the initial 0.10 second of the QRS complexes of sinus origin is polyphasic and of low voltage. A small R wave in the right precordial lead is followed by a deep, wide S wave.





Fig. 1 Top. Posteroanterior roentgenogram of the chest showing hemisphere of calcific material at cardiac apex. *Bottom.* Right anterior oblique thoracic roentgenogram. Note shadow indicative of calcific deposit in bulge at apex of cardiac silhouette.

During the terminal 0.06 second of the QRS interval the mean vector is oriented leftward and superiorly.

Whether the intraventricular block is considered to be post infarction in type or to be left bundle branch block, the marked deformity of the initial component of the QRS complexes in the left precordial leads and in Lead I and aVL strongly supports the presence of a large transmural anteroseptal scar.[8]

Discussion

Epstein[1] in 1953 summarized data on calcified cardiac aneurysms previously reported. Among 37 instances of myocardial calcification, 26 were calcified ventricular aneurysms. In 15 of these 26 cases historical evidence of acute myocardial infarction existed. Survival after this acute episode ranged from 5 to 20 years.

Harburg[2] reported survival for 28 years after initial myocardial infarction in a patient who had calcified ventricular aneurysm.

Prolonged survival after myocardial infarction and the presence of ventricular aneurysm are probably interdependent. Since biologic calcification requires a period of years for its accomplishment, only the patient with an aneurysm who survives for several years *can have* roentgenographically

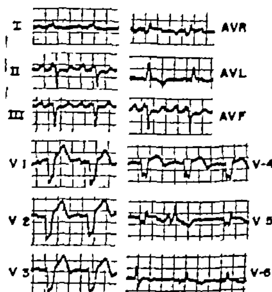


Fig. 2 Electrocardiogram recorded on May 22, 1961. The second ventricular complex in Lead aVL, the first and third complexes in Lead V4, and the second and third complexes in Lead V are of sinus origin, as are all complexes in all other leads.

demonstrable calcification of that aneurysmal wall.

Electrocardiographic changes of the kind encountered in the case here reported are commonly associated with large transmural myocardial infarcts which involve the anteroseptal region of the left ventricle. This conclusion was supported by results of a study[3] of 39 cases, in all of which there were intraventricular blocks of the left bundle branch block type and myocardial infarcts confirmed at necropsy. Among these 39 cases, 8 had significant Q deflections in Lead I. In each of these 8 cases a large transmural anteroseptal myocardial infarct was present, which was also the finding in 9 cases in which there was a Q deflection, an rsr' or a notched upstroke of R in Lead V_6.

Intraventricular block in such cases may have resulted from postinfarction block at the parietal level; on the other hand it may have resulted from interruption of conduction through the left bundle branch. Criteria for distinguishing these two forms of intraventricular block are imperfect. The term "left bundle branch type" is intended to denote a heterogeneous electrocardiographic category and not a precise anatomic lesion.

Summary

1. Data are presented on a patient who had a calcified aneurysm of the left ventricle and who had survived for 17 years after the episode of acute myocardial infarction which eventuated in the aneurysm.

2. Electrocardiographic changes were those of intraventricular block of the left bundle branch type combined with anteroseptal myocardial infarction.

3. Correlation between predicted location of the scar as derived electrocardiographically and the site of the lesion as delineated by calcific deposition in the aneurysmal wall was acceptably precise.

REFERENCES

1. Epstein, F. H. Calcified ventricular aneurysms. Am. Heart J. 46:150, 1953.
2. Harburg, W. J. Calcified cardiac aneurysms, Brit. Heart J. 19:435, 1957.
3. Rhoads, D. V., Edwards, J. E., and Pruitt, R. D. The electrocardiogram in the presence of myocardial infarction and intraventricular block of the left bundle-branch block type: a clinical pathologic study. Am. Heart J. 62:735, 1961.

Massive pericardial effusion in a patient with myocardial infarction

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Marked or massive pericardial effusion in myocardial infarction is certainly most uncommon It is not generally considered or discussed in relation to patients with myocardial infarction nor is myocardial infarction generally considered in the differential diagnosis of massive pericardial effusion. Massive pericardial effusion however may happen in myocardial infarction and the present case report demonstrates it in the extreme.

Case report

A 69-year-old white woman entered St Vincent's Hospital on Aug 29 1960 complaining of weakness and shortness of breath which had been present for 2 months. She had been well until June of 1960 at which time she had an acute febrile illness while visiting in upstate New York She was admitted to a local hospital but left within 24 hours. She returned to her home in New York City but continued to notice weakness this was gradually followed by swelling of the ankles and increasing orthopnea. Prior to this time she was accustomed to climbing two flights of stairs daily without discomfort. She was seen by a private physician who gave her "heart pills," which she took for 1 week before discontinuing them because of palpitations. She had severe anterior chest pain for 1 day approximately 1 month prior to hospitalization. Because of increasing dyspnea, orthopnea, and edema of the ankles she came to the hospital.

Past history On June 15 1960 she bled quite heavily from the vagina. A similar episode had occurred in 1959

A left nephrectomy was performed at another hospital in 1956, because of a "cyst." There was difficulty in controlling bleeding during the procedure, and one blood transfusion was given. After this hospitalization she had hepatitis. Recovery was uneventful.

A diagnosis of diabetes mellitus was made in 1957 but no therapy had been required during the past year

In August, 1959 she was admitted to St. Vincent's Hospital because of multiple purpuric spots of the lower extremities. The spleen was palpable 10 cm. below the left costal margin The platelet count was 36,800. She was considered to have a hypersplenic syndrome secondary to postnecrotic cirrhosis. Recovery from this illness was complete.

Physical examination. The patient was a slender pale, white woman in mild respiratory distress. Temperature was 101 F pulse 120 per minute, respirations 22 per minute, and blood pressure 154/84 mm. Hg The fundi revealed moderate arteriolar narrowing There was distention of the neck veins, and crepitant râles were present at both lung bases. A diastolic gallop rhythm was heard along the left sternal border A pericardial friction rub was present in the fourth left intercostal space. There were no murmurs. The heart sounds were of fair intensity The spleen was palpable 8 cm. below the left costal margin. There was a large ecchymotic area on the right buttock. Numerous areas of brownish discoloration were noted over the pretibial areas. One-plus pretibial edema was present. The pelvic examination gave findings which were within normal limits, except that a small amount of red blood was seen at the urethral meatus.

Laboratory data. When the patient was admitted to the hospital, the hemoglobin was 10.2 Gm. per 100 c.c. The hematocrit was 34 per cent; the white blood cell count was 4 900 cells per cubic milliliter The white blood cell differential count was normal. Later during her hospital course the white blood cell count gradually rose to a maximum of 28,000 cells per cubic milliliter At this time the differential count showed 88 per cent polymorphonuclear cells,

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Fig. 1. Chest x-ray film showing massive pericardial effusion.

10 per cent "band" forms, 1 per cent lymphocytes, and 1 per cent monocytes. Repeated urinalyses during the hospital course showed varying amounts of albumin (one plus to four plus) and persistent microscopic hematuria. The bleeding and clotting times were normal on repeated testing throughout the hospital course. The prothrombin time (Quick one-stage procedure) was normal at 18 seconds. The platelet count was 133,000 platelets per cubic millimeter. The blood urea nitrogen was 27 mg. per cent at the time of admission, and this gradually rose during the hospital course to a maximum of 83 mg. per cent. The fasting blood sugar was 193 mg. per cent (the patient was known to be diabetic). The SGOT and SGPT were repeatedly normal.

The serum electrolytes, in milliequivalents per liter, were as follows: sodium 137, potassium 4.4, chlorides 101, bicarbonate 34. During the hospital course, as the patient developed more severe congestive heart failure, the values, in milliequivalents per liter, were: sodium 122, potassium 6.0, chlorides 103, bicarbonate 25. The Hanger test was 4 plus. The antistreptolysin-O titer was 166 units. The Kahn test was negative. Four lupus erythematosus preparations were negative.

Pericardial fluid. The pericardial fluid was dark red in color and contained 3,000 white blood cells per cubic milliliter, of which 97 per cent were lymphocytes. The hematocrit of the pericardial fluid was 1 mm. Microscopic study of the pericardial fluid was negative for tumor cells. Cultures of each specimen of pericardial fluid showed no organism. A smear of each specimen of pericardial fluid showed no acid-fast bacilli. A tuberculin skin test was negative. Complement fixation tests and hemagglutination tests for influenza viruses done by the New York State Board of Health were negative initially and after a 10-day interval.

The electrocardiogram showed normal sinus rhythm. There were T wave changes of a nonspecific variety. The chest x-ray films showed massive pericardial effusion (Fig. 1).

Hospital course. The patient was kept at bed rest. The dyspnea persisted. A chest x-ray film revealed massive enlargement of the cardiac shadow, minimal pulmonary congestion, and a small pleural effusion at the right base. On Sept. 1, 1960, the venous pressure was 120 mm. saline, and the circulation time (sodium succinate) was 20 sec. Pericardiocentesis, performed on the same day, was productive of 450 c.c. of thin red fluid. After this there was considerable amelioration of dyspnea as well as improvement in the heart sounds. On the next day 400 c.c. of thin red fluid was aspirated, after which procedure the chest x-ray film revealed a considerable diminution in cardiac size. Nonetheless, dyspnea on minimal exertion persisted. On Sept. 6, 1960, a final pericardial tap was attempted, and only 10 c.c. of brownish fluid was obtained. The patient's appetite became increasingly worse, and she became intermittently lethargic. On Sept. 9, 1960, prednisone, 80 mg. daily, was begun. However, her pericardial friction rub and gallop rhythm persisted. Lethargy and dyspnea increased. She was pronounced dead on Sept. 24, 1960, her twenty-sixth hospital day.

Autopsy findings. The pericardial sac was distended with fluid and contained 150 c.c. of the type of fluid described. There were large areas of fresh fibrinous exudate on the pericardium. There were no adhesions. The heart and pericardium weighed 500 grams. The epicardial surface of the heart was grayish in color and nonglistening. The left ventricle was enlarged. The endocardial surface was smooth and glistening. The valves were normal. In the left ventricle was a large posterior wall infarction which extended from endocardium to epicardium, but which did not involve the septum. The coronary arteries showed extensive atheromata. There was a recent thrombus which occluded the lumen of the right coronary artery near its origin. The liver weighed 670 grams and had a finely granular surface. On cut section the normal architecture could not be seen. The portal vein was thrombosed, as was the splenic vein. The spleen weighed 500 grams. It was unremarkable grossly. The remainder of the gross examination of the viscera showed no abnormalities.

Microscopic examination of the organs revealed the following: the epicardium was covered with a thick layer of fibrin in which polymorphonuclear leukocytes were present. In the myocardium of the posterior wall of the left ventricle there were various stages of myocardial infarction which varied from areas of fibrosis to areas of fresh necrosis.

Microscopic examination of the pericardium revealed thickening and fibrosis. There were many small granulomata scattered throughout. In the liver some of the portal areas were enlarged, irregular, and fibrotic. Mild passive congestion was present. The bone marrow was normal. The remainder of the microscopic examination showed nothing remarkable.

Discussion

What could be the etiology of this massive pericardial effusion? The usual causes of pericarditis such as tuberculosis, tumor, viruses, and bacteria could not be implicated in this patient. The uremic state was not present at the time of her hospitalization, and no evidence was found of acute rheumatic fever or cholesterol pericarditis.

This patient's pericardial fluid was light red in color, and its hematocrit reading was 1 mm. This is not hemopericardium or the bloody pericardial effusion which occurs in approximately 4 per cent of patients with myocardial infarction.[1]

Even though this patient at one time had a tendency to bleed, it was not present when she was hospitalized. Since the fluid was far from bloody, one cannot say that the pericardial effusion was due to a generalized bleeding disorder.

We can advance no etiology to account for the massive pericardial effusion in this patient other than to state that this case may be an example of the pericarditis which follows a myocardial infarction.

Pericarditis associated with myocardial infarction is generally thought of in terms of a fleeting pericardial friction rub which is often missed. Recently Dressler[2] has described and emphasized a severe type of pericarditis which occurs shortly after the onset of myocardial infarction. His patients had recurrent pericarditis, and evidence of pericardial effusion was believed to be present in 62 per cent of them. However, this was confirmed in only 3 patients. Even in these patients the volume of the pericardial effusion was relatively small as judged by the reproduced x-ray films. The usual features of the "postmyocardial infarction syndrome" consist of chest pain due to pericarditis, small pericardial effusion, fever, and protracted clinical course occurring in a patient who has had a transmural myocardial infarction. Except for the fact that (1) we were not aware that our patient had had a myocardial infarction, and (2) the volume of her pericardial fluid was far greater than that which has been reported, our patient's condition could possibly be an example of this syndrome.

It is our belief that the pericardial effusion in our patient was associated with the myocardial infarction, as emphasized by Dressler. On the other hand, it is possible that our patient had two disorders, namely, virus pericarditis and myocardial infarction. It seems impossible from the information we have at hand to settle this point clearly. Case reports which indicate the occurrence of such a combination of disorders are not to be found in the literature.

Case reports of massive pericardial effusions in patients with myocardial infarction are quite rare, except for those which are associated with rupture of the myocardium and occur as "hemopericardium." These patients, however, have grossly bloody fluid. In the absence of rupture of the myocardium, we have been able to find only one similar example of massive pericardial effusion.[3]

Summary

A patient with a transmural posterior myocardial infarction is described. The striking clinical feature of the patient was a massive pericardial effusion. No explanation for this degree of effusion is known. Only one similar experience is described in the literature.

REFERENCES

1. Conrad, F. G., and Rothermich, N. O.: A clinicopathological study of acute myocardial infarction and the role of anticoagulation therapy, A.M.A. Arch. Int. Med. 102:421, 1959.
2. Dressler, W.: The Postmyocardial infarction syndrome, A.M.A. Arch. Int. Med. 103:28, 1959.
3. Nichol, E. S.: Large pericardial effusion complicating acute coronary thrombosis, Ann. Int. Med. 11:[illegible]1900, 1938.

Iatrogenic parasystole and interpolated premature ventricular beats

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Parasystole is a term used to describe an arrhythmia that is interpreted as being due to the presence and to the interaction of two rhythmic active pacemakers within the heart. Kaufmann and Rothberger's[1] classic studies form the experimental basis for this concept. Singer and Winterberg[2] were the first to invoke this concept to explain an otherwise puzzling arrhythmia encountered in man. The presence of two active pacemakers within the heart and their interaction is vividly illustrated in the following two cases in which pacemakers were implanted to prevent recurrent and disabling Adams-Stokes attacks.

Fig. 1 is from a 65-year-old man who had been subject to frequent and medically uncontrollable Adams-Stokes seizures due to recurrent prolonged ventricular standstill.

The P waves can be seen at a regular rate of 49 a minute. The electrical pacemaker signal is clearly seen as a sharp vertical line at a regular rate of 58 a minute. Ventricular complexes (1, 2, 3, 4, 5, 9, 10, 11, 12, 18, 19, 21, 22, 23) are excited by the electrical pacemaker whenever it falls outside the absolute refractory period of the sinus-produced ventricular complex. Similarly, the sinus impulse excites ventricular complexes (6, 7, 8, 14, 15, 16, 17) whenever it falls outside the absolute refractory period of the electrically induced ventricular complex. This arrhythmia is iatrogenic parasystole with simple interference.

The patient has remained free of symptoms and is unaware of irregular heart action. Indeed, even his physician thought that the patient's rhythm was entirely controlled by the pacemaker.

Fig. 2 is from a 67-year-old man who had had frequent, recurrent disabling Adams-Stokes seizures due to cardiac standstill which was medically uncontrolled and presumably due to hypoaldosteronism.

The basic rhythm is complete heart block, except possibly for a rare ventricular capture (note different contour of complex 8 in Lead I). A sinus tachycardia is present with P waves occurring at a regular rate of 115 a minute. The basic idioventricular rate varies from 59 in one lead to 65 in others. Electrically induced ventricular complexes occur at a regular rate of 56 a minute.

In the last row, parasystole with simple interference is present. The third ventricular complex is different from and intermediate in contour to the idioventricular and the electrically induced ventricular complexes. It is to be noted that the expected origins of each ventricular complex fall outside the absolute refractory period of the other. Therefore, each can excite the ventricle. Together they produce a fusion beat. A slightly fused ventricular complex is also seen in Fig. 1

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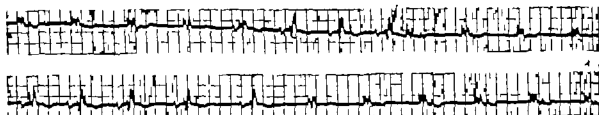


Fig. 1. Iatrogenic parasystole. See text for discussion.

Fig. 2. Iatrogenic parasystole and interpolated premature beats. See text for discussion.

(note slightly aberrant complex 1 in row 2 preceded by atrial and electrical pacemakers).

It is to be noted that a pause clearly seen before the last ventricular complex in the first row usually follows an electrically induced ventricular complex. However, in some instances the basic idioventricular rhythm is not disturbed by the interposition of an electrically induced premature ventricular beat. This is clearly seen between the second and third idioventricular beats of the third row as well as elsewhere. Such an event occurs only if the electrically induced premature beat occurs very early in diastole or at the very termination of electrical systole. An interposition of a ventricular premature beat between two dominant beats, the basic rhythm of which is not disturbed, is called an interpolated ventricular premature beat.

This arrhythmia was asymptomatic. Two months later the electrical pacemaker completely controlled ventricular excitation.

Discussion

Parasystole and interpolated premature beats have in common the fact that the centers from which impulses arise may not interfere with each other.

A protection block of the parasystolic center from the spread of excitation from the dominant center and an exit block from the parasystolic center have been postulated to explain the persistence of the activity of the two centers. Because protection block is difficult to reconcile with present physiologic knowledge, Scherf[3] has postulated that exit block is always present when the manifest parasystolic rate is slow and does not completely control the ventricular rate. This theory is based upon the demonstration of abrupt doubling of the manifest parasystolic rate.

An interpolated premature beat is explained by the assumption that the dominant pacemaker is protected from or is refractory to the ectopic beat whereas the refractory state of the conducting system and the chamber has already terminated when the next dominant impulse stimulates them. Such a train of events is rare in atrial premature beats. Scherf and Schott[4] deny the existence of interpolated atrial premature beats in man. Katz and Pick[5] state that they do occur. They illustrate an arrhythmia that they so interpret although other interpretations not relevant to this discussion are tenable. Interpolated ventricular premature beats occur in sinus rhythm when the sinus rhythm is slow and the premature ventricular systole appears early in diastole. Under such circumstances the assumption is made that the refractory period of the conduction system and that of the ventricles have terminated when the next previously protected or refractory sinoauricular impulse arrives.

Wolferth[6] states that in idioventricular rhythm the state of affairs becomes very unfavorable for interpolation because of the comparative accessibility of the pacemakers to the excitatory wave of the premature beat. Nevertheless, he admits that interpolation is possible and should occur if the idioventricular pacemaker is protected from (or refractory to) the premature beat and the conducting tissues between the pacemakers recover rapidly enough to transmit the next excitatory wave.

On the other hand if a naturally occurring parasystolic focus or indeed any abnormal naturally occurring pacemaker resembles the electrical pacemaker then neither protection nor exit block has to be assumed. For under these circumstances the anatomic substrate like the artificial electrode exists at all times during the cardiac cycle but its ingravescent stimulating products may be active only during part of the cycle.

Summary

1. Electrocardiograms from two patients with implanted pacemakers are described which illustrate iatrogenic parasystole and interpolated premature ventricular beats.

2. The mechanisms of their formations are discussed.

REFERENCES

1. Kaufmann, R., and Rothberger C. J. Beitrage zur Kenntnis der Entstehungsweise extrasystolischer Allorhythmien, Ztschr. ges. exper. Med. 5:349 1917
2. Singer R., and Winterberg, H. Extrasystolen als Interferenzerscheinung, Wien. Arch. Inn. Med. 1:391 1920
3. Scherf D. and Bornemann, C. Parasystole with a rapid ventricular center. Am. Heart J. 62:320 1961.
4. Scherf D. and Schott, A. Extrasystoles and allied arrhythmias New York, 1953 Grune & Stratton, Inc., p. 90
5. Katz, L. N. and Pick, A. Clinical electrocardiography Part I The arrhythmias, Philadelphia, 1956 Lea & Febiger p. 231 Fig. 111.
6. Wolferth, C. C. So-called interpolation of extrasystoles during idioventricular rhythm. Am. Heart J. 5:482, 1930.

Clinical pathologic conference

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Clinical review

Summary. The patient, a 59-year-old white housewife, was hospitalized on June 21, 1960, because of gastrointestinal bleeding which had been present for 2 months; she died 1 month later in congestive failure.

First admission. The patient was admitted to St. Luke's Hospital in 1953, complaining of difficulty in walking and speaking which had been present for 12 hours. She had had heart disease for 4 years; this had been treated with digitalis. Her present complaints developed after a sudden episode of intense headache which was localized in the right frontal region. Objectively and subjectively her movements were clumsy, with numbness of the hands, particularly the right one.

Past history. In 1919 the patient had an ulcer of the left cornea which was ascribed to herpes simplex, and a tonsillectomy in 1943. She had no definite history of rheumatic fever.

Family history. The patient's parents both died in old age of cardiorenal disease.

Physical examination. The temperature was 98°F., pulse was 92 per minute, respirations were 16 per minute, and blood pressure was 140/70 mm. Hg. The pulse was extremely irregular. An opacity of the left cornea, with fixation of the iris and drooping of the left eyelid, was noted. The heart was enlarged to the left. There was irregular irregularity of the cardiac beat. The first sound was snapping at the apex; the second sound was split at the base and was heard best at the third left intercostal space. A Grade 3 diastolic murmur which radiated to the mid-precordial region was heard at the apex. The deep tendon reflexes were increased on the right. The Babinski reaction was equivocal on this side.

Laboratory data. Hemoglobin was 13.6 Gm. per cent; white blood cell count was 8,650 per cubic millimeter with 65 per cent polymorphs, 5 per cent band forms, and 30 per cent lymphocytes. Kahn and urine tests were negative, and blood sugar, nonprotein nitrogen, and prothrombin levels were normal. Sedimentation of the blood was 29 mm. in 60 minutes. An electrocardiogram showed auricular fibrillation with right axis deviation and a low QRS complex with an interval of 0.08 second (Fig. 1).

Hospital course. After rapid clearing of her complaints, the patient was discharged in 6 days on a low-salt diet, diuretics, and digitalis.

Second admission (May 31 to June 14, 1960). The patient was readmitted 7 years later complaining of nausea, vomiting, and diarrhea which had been present for 2 days. She ascribed this to the eating of unusual food. However, in the prior week she had noted edema of the ankles, orthopnea, and headaches.

Physical examination. The temperature was 97.4°F., pulse was 87 (irregular), respirations were 16, and blood pressure was 110/60 mm. Hg. The heart was enlarged to the left anterior axillary line. Grade 2 systolic and mid-diastolic murmurs were heard over the precordium. The liver was enlarged (3 fingerbreadths), and there was edema (1+) up to the level of the knees. The left eye remained as before.

Laboratory data. Hemoglobin was 8 Gm. per cent; red blood cell count was 3.04×10^6/mm.^{3}; white blood cell count was 12,850 with 67 per cent polymorphs, 19 per cent band forms, 9 per cent lymphocytes, and 9 per cent monocytes. Urine was normal. Feces contained occult blood (4+ guaiac). The sedimentation rate was 24 mm. per hour. Chemistry of the blood showed Cl, 99 mEq./L.; Na, 142 mEq./L.; K, 4 mEq./L.; CO_2, 29 mEq./L. The blood urea nitrogen was 19 mg. per cent.

Hospital course. During hospitalization, the patient's anemia and gastrointestinal bleeding were studied. The red cell constants were: hematocrit, 28 per cent; mean corpuscular volume, 89; mean corpuscular hemoglobin, 26; mean corpuscular hemoglobin concentration, 30. The Diagnex blue test was negative. The serum iron was 21 micrograms. The cobalt 60 vitamin-B absorption test was normal. Blood smears showed polychromatophilia, anisocytosis, microcytosis, and slight spherocytosis. Radiographic studies of the gastrointestinal tract showed diverticula in the descending and sigmoid colon. Two upper gastrointestinal series were nega-

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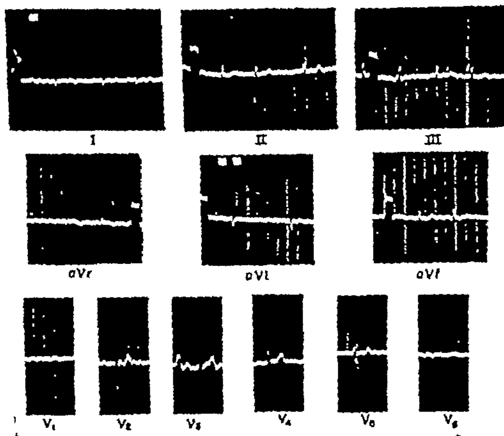


Fig. 1. Electrocardiogram in 1955 showing auricular fibrillation and low QRS complexes.

tive. An electrocardiogram showed QRS of 0.06 second and Q-T of 0.32 second. Auricular fibrillation and rare ectopic ventricular beats were noted. This suggested right ventricular hypertrophy and digitalis effect.

Final admission (J ne 22 to July 22, 1960). The patient was readmitted 1 week after discharge for further study of her continued melena and accompanying increase of dyspnea and fatigue.

Physical examination. The temperature was 97°F, pulse was 84 (irregular), respirations were 24, and blood pressure was 104/70 mm. Hg. The patient was thin, pale and dyspneic. Moist râles were heard in the base of each lung. The heart was enlarged, with the point of maximal impulse to the left of the midclavicular line in the sixth intercostal space. The sounds were grossly irregular. The pulmonic second sound was greater than the aortic second sound. A Grade 3 blowing systolic murmur and a diastolic murmur were heard over the apex of the heart. The liver was palpated 2 cm. below the costal margin.

Laboratory data. The red blood cell count was 6.4 million/mm., white blood cell count was 19,100/mm., platelets were 142,000/mm., hematocrit was 26 per cent, sedimentation rate of the blood was 25 mm. per hour. Chemistry of the blood showed K, 4 mEq./L., blood urea nitrogen, 21 mg. per cent. Prothrombin time (one-stage) was 41 per cent.

Hospital course. The patient had intermittent diarrhea and melena without fever for her entire hospital course. Liver function tests showed bilirubin (total) 0.79 mg. per cent, bilirubin (1 minute), 0.19 mg. per cent, thymol turbidity 0.6, ammonium sulfate turbidity 1.3, cholinesterase 0.25, A/G = 3.7/2.7, alpha globulin, 1.3 Gm. per cent, alkaline phosphatase 3.3 units. Multiple transfusions with both whole blood and packed erythrocytes were given, with occasional complications of d spnea and episodes of confusion, but without beneficial effect on the anemia and low prothrombin levels. A repeated gastrointestinal series showed no significant evidence of disease. On June 27, flare-up of the left eye with ciliary flush and corneal haziness was treated with very slight success by antibiotics. Fundic examination at this time showed a normal right fundus and evidence of a yellowish patch of old chorioretinitis below the left disc. An electrocardiogram at this time showed auricular fibrillation and little change from that of the previous admission. On June 31, the patient was found to ha soreness of the tongue and a beef red color of the entire oral mucosa. This was treated with perborate. On July 14, a string and small bag were passed into the small bowel and a bleeding point in the upper jejunum or lower duodenum was successfully demonstrated. In the process the patient had severe dyspnea and irregularity of the pulse with the appear



Fig. 2. Lesion of skin which shows angioblastic tissue, fusiform cells, slits, and vascular spaces with surrounding erythrocytic diapedesis.

…ce of basal pulmonary râles. An electrocardiogram showed auricular fibrillation with frequent, multifocal, ectopic ventricular beats. Marked QRS changes suggestive of anterior myocardial infarction were noted, but lack of standardization prevented accurate evaluation of the record. On July 15 purplish, raised elevations of the skin, which measured as much as 1.1 cm., began to develop, first over the scapulae and abdomen and later over the eyebrows and thighs. Mentally the patient deteriorated. Laboratory studies at this time showed continued severe anemia and low prothrombinemia. The serum chloride was 94 mEq./L., sodium, 136 mEq./L., potassium, 4.1 mEq./L., phosphorus, 1.5 mg. per cent, alkaline phosphatase 4.3 units. The blood urea nitrogen was 45 mg. per cent. For the remainder of the patient's life the skin lesions showed progression, and she became gradually more dyspneic until death, 1 month after admission.

Discussion

DR. PAUL. This is clearly an unusual case. Evidently heart disease was first detected when she was 48 years old. At the age of 52 she had what seems to have been a cerebral embolus and there were physical findings of atrial fibrillation, a loud apical diastolic murmur with an accentuated first heart tone, minor reflex changes, and right axis deviation by the electrocardiogram. It appears that she then did well for 7 years until the age of 59 when she abruptly developed symptoms of congestive heart failure with headache, vomiting, and diarrhea. She now had a large heart, still with a diastolic murmur, and some hepatomegaly, and apparently a severe iron-deficiency anemia, with occult blood in the stools. No chest x-ray report is given, but gastrointestinal x-ray examinations were negative, and the electrocardiogram showed right ventricular hypertrophy. In the 7 week period until her death I note a progressive downhill course without fever, but with diarrhea and melena. A low prothrombin level and a lowered serum albumin were present. In the last week of her life upper gastrointestinal bleeding was evidently demonstrated, and purplish skin lesions developed. The electrocardiogram may have shown an anterior myocardial infarct, and uremia appeared.

My first diagnostic consideration is rheumatic heart disease with predominant mitral stenosis, atrial fibrillation which probably had been present for 11 years, an old cerebral embolism, and terminal congestive heart failure. I believe that this is a reasonable diagnosis in view of her long history of heart disease, the murmur which seems to be indicative of mitral stenosis (the systolic phase may well be related to the anemia), the character of the heart sounds, and the electrocardiogram. Hepatic congestion may at least partially explain the laboratory findings. Rheumatic heart disease by itself does not adequately explain the chronic anemia, gastrointestinal difficulties, or the skin lesions. The anemia might be due to bacterial endocarditis, but I find this diagnosis hard to accept in the absence of any fever, petechiae, or splenomegaly, etc., and furthermore this is a lot of anemia for bacterial endocarditis. The diarrhea could be due to digitalis intoxication, but this seems highly unlikely over such a long period of time and would not explain the melena. I cannot explain the skin lesions as being due to rheumatic heart disease. I have considered explanations other than rheumatic mitral stenosis for

the evidence of left atrial disease and am unable to accept them. Thus the long 11 year history would seem to make a primary left atrial tumor most unlikely and would exclude secondary tumor invasion of the heart. I cannot entirely rule out the rare possibility of a congenital mitral stenosis.

We shall have to cast around for other disease entities which may in association with mitral stenosis give this clinical picture. How about a tuberculous enteritis amoebiasis, or typhoid fever? If present they were not confirmed by gastrointestinal x-ray examinations or fever and I believe that since stool cultures and examination for parasites must have been done at some time, these diagnoses are likewise highly improbable. Histoplasmosis appears to be a possibility since it may cause anemia diarrhea and purpuric lesions but absent here are the fever splenomegaly and lymphadenopathy as well as the leukopenia and pulmonary infiltrates which I would like to see.



Fig. 3 High-power view of undifferentiated portions of lesion of the skin, showing anaplastic cells with little formation of lumina.

Neoplasms already referred to in relation to the heart must be thought of. Carcinoid syndrome of course may be accompanied by fibrotic thickening of the endocardial surfaces of the right side of the heart and to a lesser degree of the left, and certainly signs of gastrointestinal involvement because the carcinoid tumor is usually primary in the ileum encircling it and producing symptoms which include diarrhea. Carcinoid tumors also may heavily infiltrate the liver. However I have seen the carcinoid syndrome and it never looked like this. No flush was described. No signs of pulmonary or tricuspid valvular disease are mentioned and I have not observed significant melena with the carcinoid syndrome although these tumors do ulcerate and cause modest bleeding. There is no x-ray evidence of any of the usual gastrointestinal malignancies.

Ulcerative colitis appears to be excluded by the x-ray examination. This does not resemble a Schönlein Henoch purpura, and I do not find in her record evidence which indicates a severe drug reaction, such as mercurialism.

I am intrigued by the possibility of amyloid disease. Cases of involvement of both the gastrointestinal tract and heart have been described. This disease may even cause electrocardiographic changes which simulate myocardial infarction and of course it can cause diarrhea. I have also seen amyloidosis with such involvement of the small arteries that acute duodenal ulceration occurred. The liver may also be affected. I wonder very much whether this patient therefore did not have an old rheumatic mitral stenosis and an independent amyloid disease, with cardiac amyloidosis hepatic infiltration involvement of the small intestine and actual ulceration with bleeding. Purpura can be seen also although the description of the skin lesions does not sound 100 per cent like purpura. This is the best that I can do although I regret having to make two diagnoses.

DR. AYER The first material received from this patient for histologic study was a biopsy from one of the skin lesions (Figs. 2 and 3). Beneath a slightly acanthotic epidermis there is an irregular mass of



Fig 4 Heart viewed from the posterior aspect showing the large tumor within the left atrium

angioblastic tissue This is composed of mixed rounded and fusiform cells which occur as whorled masses that contain slit like spaces or as the lining and cover of vascular spaces of varying size Silver stains indicate that the predominant round cells occur within the basement membranes and the more fusiform cells are external to them In general the vascular spaces predominate superficially beneath the epidermis, and the more undifferentiated masses of angioblastic cells, with minimal formation of lumina, occur in the deeper tissues The cells are large with vesicular nuclei and are closely spaced Irregularity in size shape and staining quality with the occurrence of atypical mitoses is variable being more prominent in the more primitive undifferentiated areas. The connective tissue stroma is edematous and moderately infiltrated by lymphocytes histiocytes and fibroblasts Tiny extravasations of erythrocytes and deposits of hemosiderin occur in the stroma in the vicinity of the larger sinusoidal vascular spaces. The tumor has no capsule, and the lesion fades into the surrounding stroma. The picture described is identical to that of angiosarcomatous change in Kaposi s disease.

At autopsy the heart was enlarged chiefly on the left side (Fig 4) The left atrium was found to be distended and its wall was thinned by a huge intraluminal mass which measured 8 by 6 by 4 cm. This was firmly attached to the superior aspect of the atrial endocardium It bulged the interatrial septum to the right and lay partially in the dilated mitral orifice like a ball valve A similar but separate, mass which measured 6 by 4 by 1 cm. was found in the superficial tissues over the anterior aspect of the right ventricle. Both masses had a variegated purple and tan color Numerous blood filled spaces were present Areas of yellow necrosis were scattered through the tumor The luminal aspect of the intra-atrial mass was coated by layers of blood clot.

Microscopically the tissue which composes each mass is angioblastic and similar to that seen in the deep portions of the tumor of the skin (Fig 5) Masses of endothelial and perithelial cells of an embryonic type with numerous atypical mitotic figures are juxtaposed with more differentiated zones in which occur vascular sinuses filled with blood The stroma is composed of edematous fibrous tissue which is densely infiltrated by polymorphonuclear leukocytes lymphocytes, and macrophages. At the point of attachment of the intra atrial mass the tumor is seen to be limited to the subendocardial tissue but nests of tumor within vascular spaces can be seen penetrating the stretched and thinned atrial muscle. Over and partially mixed with the luminal aspects of the intra atrial tumor laminations of antemortem thrombus of varying age occur

Numerous polypoid masses composed of mottled purple pink and tan tissue were found in the mucosa of the stomach duodenum and proximal jejunum. These masses were fleshy in consistency and measured up to 3 0 cm in diameter Two of the jejunal masses were ulcerated with the occurrence of blood clot on the surface

Microscopically these masses are composed of malignant angioblastic tissue similar to the lesions of the heart and skin (Fig 6) They involve the mucosa and submucosa of each organ with intravascular extensions into the muscularis. The surfaces of those from the jejunum show



Fig 5 Attachment of angioblastic tumor to the endocardium of the left atrium.

ulceration with exposure of the vascular sinuses to the lumina and evidence of recent hemorrhage It is impossible to determine whether these lesions are primary or secondary in type

Definite evidence of tumor thrombus embolization was found in the lungs liver spleen kidneys, adrenals, and brain Emboli of tumor thrombus were found in the small arteries, juxtaposed to areas of infarction in these organs. It is believed that these emboli originated from the tumor in the heart

Careful gross and microscopic examination of the heart failed to produce any evidence of rheumatic carditis. A few small stellate scars occurred in the upper part of the anterior wall of the left ventricle and suggested old healed infarction possibly of embolic origin A small fibrous scar was found in the left cerebellum and can be correlated with the nervous manifestations which occurred in 1953 No tumor was present within the scar

This case is similar both histologically and in the distribution of lesions to the 16 cases summarized by Anthony and Koneman[1] as visceral Kaposi s sarcoma. Although technically our case should be classified as a mixed visceral and cutaneous form of the disease the late development of lesions of the skin in this patient would not have been present if the patient had died a month sooner and also the distribution of the lesions is more in keeping with that of the purely visceral disease The picture in this case is almost identical to that of the 2 cases described by Choisser and Ramsey[2] except that their patients were male and younger the lesions they described involved the right atrium of the heart and the total course of the disease was shorter

DR. PAUL Was there no evidence of rheumatic heart disease? It seems difficult to believe that the patient s cardiac complaints which had been present for 11 years could be explained by this tumor

DR. AYER Careful examination both gross and microscopic revealed no evidence of rheumatic heart disease. Kaposi s disease in all of its forms characteristi-

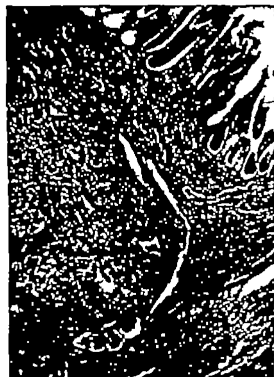


Fig 6 Angioblastic tumor in jejunum, involving both the mucosa and underlying deep tissues.

Table I

Population	*Absent Q Waves in* I, V_5, V_6 (%)	*Absent Q Waves in* I, aV_L, V_5, V_6 (%)
32 cases of "proven" septal fibrosis (adult men)	62.4	46.9
100 cases of "proven" anterior infarction (adult men)	27.0	13.0
35 men with classic angina pectoris (ages 35-72)	20.0	—
413 clinically "healthy" railmen (ages 40-59)	20.1	15.7
142 clinically "healthy" women (ages 40-59)	17.6	—
1,713 Italian rural workers (ages 40-59)	3.2	2.0
1,676 Finnish rural workers (ages 40-59)	6.0	3.2

working populations. To test this question in part we have studied prevalence of the sign in several groups, anticipating that the relationships found would tell us something about the discriminative value of the sign.

Table I summarizes the results. At the outset, in an autopsy sample in which septal fibrosis was well described, the ECG sign of absent Q wave in Leads I, V_5, and V_6 was found in 20 of 32 cases. In 100 cases of "proven" anterior infarction (septal, anterior lateral) the sign occurred in 27. Seven of 35 men with classic angina pectoris had the sign. In these groups the association is sufficiently high to ...rate Burch's impressions from a similar ...ty population.

...wever, in our experience the validity of any ...gnostic criterion is highly dependent upon the composition of the population in which it is applied. This appears to hold true in the case of the absent Q wave. The table shows the high prevalence of the finding in a screened "normal, healthy" group of U. S. employees, men and women between the ages of 40 and 59. In a more heterogeneous group of 649 men, ages 20 to 60 years, a distinct age trend occurred (20-39, 1.8 per cent; 40-59, 20.1 per cent). But no such trend was found in women by age (20-39, 2.9 per cent; 40-59, 17.6 per cent). Thus, the high prevalence of absent Q waves in Leads I, V_5, and V_6 in the conventional ECG among working groups in this country and the inconsistent age and sex trends of this finding resulted in some doubt in our minds about the value of the sign in subjects outside hospital practice.

Moreover, in the compilation of these data it became apparent that observer variation in the "calling" of totally absent Q waves has to be considered (inter-observer agreement was roughly 75 per cent), and that factors of ECG technique and equipment greatly influence prevalence of the sign. It could readily be demonstrated by simultaneous oscilloscopic display that poor response characteristics of the ECG machine resulted in "false positive" signs, and very small Q waves were often obscured by thick base lines from excess temperature of the stylus. In addition, a minute Q wave in Lead V_6 could be eliminated experimentally by very small shifts in electrode position. Finally, "electrical position" in the horizontal plane (the point of QRS transition) had a marked effect on the presence or absence of Q waves.

We have examined further the question of frequency response of ECG apparatus and the occurrence of the sign in certain overseas groups studied in a collaborative program conducted by the director of this laboratory, Dr. Ancel Keys. "High fidelity" apparatus (the Swedish Elema 42, a 4-channel, jet system machine with response to 900 cycles per second) was used in studies of 3,389 men who were between the ages of 40 and 60, representing virtually the total male population of those ages in several rural areas of Italy and Finland. By all evidence obtained so far the Finnish groups have a prevalence of coronary heart disease roughly comparable to that in the United States, whereas the Italian men of corresponding age probably have much less. Among 1,676 Finns the absent Q sign was found in 6.0 per cent, and among 1,713 Italians it was found in 3.2 per cent. All figures apply to the sign as originally described, absent Q wave in Leads I, V_5, and V_6. We found no good evidence that incorporation of Lead aVL increases the specificity of the sign. In the above-mentioned groups the frequencies are distinctly lower than in the United States groups examined with conventional hot-stylus machines.*

Association of the ECG sign with other ECG abnormalities was studied, since this is germane to the question of its sensitivity. S-T depression and T wave negativity were recorded by defined criteria[4] in those with the sign and in the total groups. There was a slight excess of these "nonspecific" abnormalities in groups with the absent Q sign, as compared to the total group, but not a high degree of association between the sign and other nonspecific ECG characteristics of coronary heart disease.

Burch found left ventricular hypertrophy at

*The material in Finland was made available by Dr. Martti Karvonen, of Helsinki, and that in Italy by Professor Flaminio Fidanza, of Naples, and Professor Vittorio Puddu, of Rome. Details of these studies, as well as acknowledgments to the U. S. Public Health Service, the American Heart Association, and other organizations that gave support, will be given in publications now in preparation.

autopsy in 80 per cent of the cases of septal fibrosis. There was no association in these 3,389 working men between "left hypertrophy" by ECG amplitude criteria and the ECG sign of septal fibrosis.

From frontal plane amplitude data in our material it would appear that in many of the "positive" cases the main vector loop simply is nearly perpendicular to the frontal plane, and the magnitude of the projected initial vectors is too small to be distinguished even in recordings of high fidelity.

Obviously Q waves are best regarded not as well-defined, "yes-no" phenomena in scalar tracings, but as initial spatial vectors seen through a lead system with a considerable amount of built-in distortion. It may be that certain newer types of vectorial display from orthogonal lead information, with attention given to interrelationships between initial and other vectors, may prove helpful in elucidating this question and others raised by the conventional "Q."

In summary, the diagnostic value of an ECG sign of septal fibrosis described by Burch (absent Q wave in Leads I, V_5, V_6) was partly corroborated in an abnormal autopsy material from a hospital population. However, the high percentage of asymptomatic working persons in the United States with the sign, its unreliability as regards observer agreement, and the distinct effect on its prevalence of the response characteristics of apparatus and of recording technique render it of no value as a "minor" ECG sign of coronary disease in populations outside of the hospital.

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REFERENCES

1. Burch, G. E.: An electrocardiographic syndrome characterized by absence of Q in Leads I, V_5, and V_6, Am. Heart J. 51:457, 1956.
2. Burch, G. E., and DePasquale, N.: A study at autopsy of the relation of absence of the Q wave in Leads I, aVL, V_5, and V_6 to septal fibrosis, Am. Heart J. 60:336, 1960.
3. Evans, W., and Pillay, R. K.: Additional electrocardiographic signs of cardiac pain, Brit. Heart J. 19:311, 1957.
4. Simonson, E.: Presence or absence of certain deflections, p. 132, *in* Differentiation between normal and abnormal in electrocardiography, St. Louis, 1961, The C. V. Mosby Company.
5. Blackburn, H., Keys, A., Simonson, E., Rautaharju, P., and Punsar, S.: The electrocardiogram in population studies. A classification system, Circulation 21:1160, 1960.

Digitalis dosage—individualized or confused?

Any student who consults popular texts of medicine or cardiology in order to find the proper dose of digitalis compounds will find curious discrepancies in the amounts recommended by different authorities. A few examples from current books will illustrate this.

In the case of a patient who is to be digitalized orally with digitalis leaf, expected dosages range from 1.2 Gm. in 24 hours,[14] through 1.5 Gm. and 1.0 to 1.5 Gm.[26] in 24 to 48 hours, to 1.5 to 2.5 Gm. in 1 to 3 days.[26] When using lanatoside C for intravenous digitalization, one group advocates an initial dose of 0.8 mg.,[14,26] followed in 4 to 6 hours by additional increments of 0.4 to 0.8 mg. Some use 1.2 to 1.6 mg. over a short period[3,16] and usually find this adequate, but others use an initial dose of 1.6 mg.[26] and give more in 6 hours if necessary. The daily maintenance dose of digitalis leaf is stated to average 0.065 to 0.1 Gm.,[26] 0.065 to 0.13 Gm., 0.1 Gm., 0.06 to 0.2 Gm.,[26] 0.15 Gm., and 0.2 Gm.[26] (the last specifically in auricular fibrillation). When digoxin is used, the recommended averages group into multiples of the one-quarter milligram tablet. The result is that average daily maintenance doses differ by 100 per cent, since some authors find 0.25 mg. to be generally satisfactory,[14] whereas others regularly use 0.50 mg.[4,21,26]

The commonly expressed idea that the proper dose of digitalis for any specific patient must be determined through an individual therapeutic trial is not adequate to explain the varying average doses used. Nor will the suggestion that "there is no average initial or maintenance dose except that which exists on paper"[22] be likely to satisfy the inquiring and critical medical student or house officer who is not yet accustomed to the confusion in this field. Perhaps it is unwise to make deductions about usual clinical practice from the lack of uniformity in recommended average dosages of digitalis in textbooks. However, it is suspected that these discrepancies are the result of important differences in the manner in which these drugs are used by different physicians. If these differences do exist, a patient in need of rapid digitalization will receive an initial dose of lanatoside C which in one case will be 0.8 mg. and in another instance 1.6 mg., depending on the convictions of the particular physician in charge. Unless there is a much wider therapeutic range than is generally supposed, the speed with which digitalization is reached will vary markedly. The fact that some doctors usually find 0.25 mg. of digoxin adequate for maintenance, whereas others use 0.50 mg., again suggests a wide therapeutic range. It is equally possible and probably more

by a review of present electrocardiographic standards in which the inadequacy of these standards is documented.

Of less immediate use but of even greater eventual importance is an excellent discussion of the sources of variability in the electrocardiogram. Knowledge of these sources has always been of great importance in electrocardiography but will become essential as more rigorous quantitative analyses are applied.

This is not a text of electrocardiographic theory. The author states his intent that this be a supplement to texts in which the theory of electrocardiography and the differentiation of various abnormalities are considered. This book is specifically concerned with the recognition of the normal electrocardiogram. The information contained is not available from any other source and should be accessible to all those who interpret clinical electrocardiograms.

For the most part, the volume is excellently organized. The foreword by Dr. Charles Kossmann describes the importance of the work and places it in perspective with reference to previous attempts to define the normal electrocardiogram. The introduction by Dr. Ancel Keys is an eloquent statement concerning the role of modern statistical methods in medical research. The text itself begins with a clear statement of the scope and objectives of the book and a chapter on principal considerations in determining normal electrocardiographic limits. A review of present standards is followed by three chapters on sources of variability in the electrocardiogram. The presentation of these sources is admirably organized under the headings of technical and biologic variability, with the latter divided into physiologic and constitutional variables. New normal standards are then presented and a separate chapter concerns the normal day-to-day variability of the electrocardiogram.

The chapter entitled "Distribution of Electrocardiographic Patterns" is written from the controversial point of view that scalar leads from any point on the body surface are projections of the spatial vectorcardiogram. This chapter will be of interest to research workers but of less interest to the clinical electrocardiographer. Chapters on the ventricular gradient, stress tolerance tests, and minor electrocardiographic changes are appropriate supplements to the material on the range of normal variation.

The last chapter concerning vectorcardiography has little to do with the major thesis of normal standards for the 12-lead electrocardiogram. In its own right this chapter is an able review of the subject. This chapter inevitably contains some controversial material. There is, for example, a statement that the vectorcardiogram is an approach to true quantitation. This statement is especially surprising in a volume largely devoted to quantitative standards for the electrocardiogram since a major limitation of the vectorcardiogram is the difficulty one has in applying practical quantitative methods to the record.

A short discussion entitled "Some Biophysical Bases of Electrocardiographic Analysis," by Dr. O. H. Schmitt, is included.

In summary, this book goes far toward filling an extremely important and practical need in electrocardiography. It should be available to all those who interpret electrocardiograms for diagnostic purposes.

Announcement

The deadline for receipt of applications for the AMERICAN BOARD OF PEDIATRICS EXAMINATION in the subspecialty of PEDIATRIC CARDIOLOGY is April 15, 1962. The written examination will be held in June 1962, and the oral examination in October 1962. The exact dates have not yet been set.

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Editorial

Paradoxical pulsation of the precordium in myocardial infarction and angina pectoris

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In 1935 Tennant and Wiggers[1] ligated a branch of the coronary artery in dogs and demonstrated that the area which became ischemic developed a paradoxical movement during systole. In other words, as the intraventricular pressure increased during systole, the ischemic area of the myocardium ceased to function or contracted very weakly, which resulted in a ballooning-out of the area rather than the inward movement which usually occurs. After a myocardial infarction the ventricular wall may develop permanent aneurysms of varying sizes in possibly as high as 38 per cent of the patients.[2] Thus, two abnormalities of the ventricular wall may result from the coronary artery disease (myocardial infarctions): (1) a true anatomic aneurysm and (2) a physiopathologic aneurysm with a paradoxical pulsation during the time when the intraventricular pressure is high. These two abnormalities have been detected in the past by several laboratory techniques. Initially, roentgenokymographic studies demonstrated the paradoxical pulsations of the left ventricular wall in patients who were known to have myocardial infarctions.[3,4] With the advent of the electrokymographic technique these studies were extended and similar findings were noted.[5,6] However, there is still some confusion concerning the significance of the electrokymographic studies because it has not yet been determined how much outward or paradoxical movement is influenced by the positional movements of the heart.

Because of the close proximity of the heart to the anterior chest wall, paradoxical movements, or "bulges," due to myocardial infarctions were more frequently demonstrable by the radiographic techniques when they occurred on the lateral and posterior aspects of the left ventricle. In 1955 Vakil[7] re-emphasized the importance of paradoxical pulsations, or bulges, due to myocardial infarctions which can be palpated at the bedside as a physical diagnostic sign. Since then, other studies have been published which have described the graphic representation (kinetocardiographic) of these paradoxical pulsations[8] and findings by palpation.[9] Thus paradoxical pulsations frequently can be detected on the anterior, anterolateral, and inferior aspects of the heart as

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well as in other areas. Additional kinetocardiographic studies of the bulges due to myocardial infarctions have been undertaken in this laboratory[16] and the initial series has now been extended to include 102 patients with both old and acute myocardial infarctions (all patients with arterial diastolic hypertension were excluded). A significant paradoxical pulsation was present in 68 per cent of the patients. There were only slight differences in frequency of occurrence between the anterior and posterior infarctions: bulges occurred in 70 per cent of the acute infarctions and in 64 per cent of the old infarctions. In general, the patients with anterior infarctions have bulges located more frequently over the anterior precordium and less frequently in the epigastric areas;* however, both types of infarction may produce recordable bulges in both areas. Although experimental and clinical evidence points to the origin of the "bulge" as presented, there are still several unanswered questions. The patients in the series[16] were carefully selected so that the only detectable heart disease was the myocardial infarction; nevertheless, one cannot exclude the fact that the so-called "bulge" may be due to causes other than a paradoxical motion of the underlying infarcted myocardium. For example, the left ventricular thrust (apex impulse) in patients with fairly pronounced left ventricular hypertrophy resembles the "bulge" noted in apical infarctions by palpation and by graphic representation. At present there is no way to determine whether the abnormality is due to paradoxical pulsation from an infarction or is the result of an outward sustained movement associated with left ventricular hypertrophy except by the simultaneous consideration of other clinical information. However, the location of the maximum impulse in most patients is of some help. The "bulge" of largest amplitude occurs more frequently at the electrocardiographic positions V_3 or V_4, whereas the maximum impulse in left ventricular hypertrophy is more often at V_5 or V_6. Sustained outward systolic movements over the precordium are also common in patients who have very large hearts and severe congestive heart failure (Class 4 cardiac) even though the heart disease may not be due to coronary artery disease. In addition, certain patients with pronounced right ventricular hypertrophy may have systolic outward movements located over the precordium which by palpation and graphic representation occasionally resemble those due to myocardial infarctions. Although it is reasonable to assume that any abnormality encountered in patients who have only infarctions is due to those lesions alone, it is also possible that some of these patients do have outward paradoxical systolic motions which are secondary to other undiagnosed cardiovascular abnormalities (for example, left or right ventricular hypertrophy) rather than the result of the infarcts. Thus it is important, particularly when palpating the precordium of patients with large hearts possibly due to left or right hypertrophy, that one carefully consider all factors before diagnosing any paradoxical motion as a "bulge" due to an infarction. With the increased trend toward surgical correction of ventricular aneurysms, added caution must be used in the interpretation of these movements. The presence of a paradoxical pulsation or "bulge" over the precordium does not necessarily indicate a true ventricular aneurysm which can be corrected by operation. At the present time there is no way to determine whether these pulsations are caused by an anatomic aneurysm or a ballooning-out of the ventricular wall during systole, similar to that described by Wiggers in the dog experiments.[1] The decision of the feasibility of surgical correction of a ventricular aneurysm must be determined with the aid of other techniques, such as radiography, fluoroscopy, or angiocardiography.

Although it appears likely that the ballooning-out of the thinned or poorly contracted ventricular wall is the mechanism for many of these "bulges," other explanations may be offered. The "bulges" may be related in some fashion to ventricular dilatation because similar traces are noted in patients with very large hearts and marked congestive heart failure regardless of the cause of heart disease. The

*These included the records from the left and right mid-clavicular line just beneath the costal margin in the epigastrium and in the mid-epigastric area just beneath the xiphoid process.

occurrence of a significant bulge in the V_2 area in patients with strictly posterior or diaphragmatic infarctions is difficult to explain solely by a bulge of the underlying myocardium.

The problem of the paradoxical pulsations in patients with angina pectoris is even more complicated. Harrison and co-workers[11,12] found that approximately 30 per cent of the patients with angina pectoris (without clinical or electrocardiographic evidence of infarctions) have precordial paradoxical pulsations even at rest. These "bulges" tend to disappear on exercise which is insufficient to produce pain but they then may become exaggerated when pain ensues. Thus these patients who had "bulges" at rest which improved with sub-pain-threshold exercise may have a chronically ischemic area which contracts poorly. On the other hand the resting bulge may represent a myocardial infarction even though the electrocardiogram is often within normal limits. However the improvement or diminution of the bulge on mild exercise is difficult to explain by this hypothesis.

It is evident that the finding of a paradoxical precordial movement in patients with coronary artery disease has a good deal of significance and is often very useful clinically in determining or verifying the underlying cardiac abnormality. In addition, such movements may appear very early in the course of the infarction even before changes are detected by electrocardiography or laboratory studies. Nevertheless, caution should be used in their interpretation since both left and right ventricular hypertrophy may be associated with similar paradoxical movements which often cannot be distinguished from bulges due to myocardial infarctions.

REFERENCES

1. Tennant, R., and Wiggers, C. J. The effect of coronary occlusion on myocardial contraction, Am. J. Physiol. 112:351, 1935.
2. Scherf, D. and Boyd, L. J. Cardiac aneurysm, M. Clin. North America 26:919, 1942.
3. Sussman, M. L., Dack, S. and Master, A. M. The roentgenkymogram in myocardial infarction. I. The abnormalities in left ventricular contraction, AM. HEART J. 19:433, 1940.
4. Dack, S. Sussman, M. L. and Master, A. M. The roentgenkymogram in myocardial infarction. II. Clinical and electrocardiographic correlation, AM. HEART J. 19:464, 1940.
5. Samet, P. Schwedel, J. B., and Mednick, H. Electrokymographic studies in aneurysm of the left ventricle, AM. HEART J. 39:749, 1950.
6. Dack, S., Paley, D. H., and Sussman, M. L. A comparison of electrokymography and roentgenkymography in the study of myocardial infarction, Circulation 1:551, 1950.
7. Vakil, R. J. Ventricular aneurysms of the heart: preliminary report on some new clinical signs, AM. HEART J. 49:934, 1955.
8. Soh, S. K., and Eddleman, E. E., Jr.: Kinetocardiographic findings of myocardial infarction, Circulation 19:531, 1959.
9. Hurst, J. W., and Blackard, E. Inspection and palpation of pulsations on the front of the chest, AM. HEART J. 56:159, 1958.
10. Davis, J. C., Langley, J. O. Dodson, W. H. and Eddleman, E. E., Jr. Clinical and kinetocardiographic studies of paradoxical precordial motion, AM. HEART J. (to be published)
11. Harrison, T. R., and Hughes, L. Precordial systolic bulges during anginal attacks, Tr. A. Am. Physicians 61:174, 1958.
12. Harrison, T. R.: Some clinical and physiologic aspects of angina pectoris, Bull. Johns Hopkins Hosp. 104:275, 1959.

The treatment of quinidine-induced ventricular fibrillation by closed-chest resuscitation and external defibrillation

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Ventricular fibrillation is probably the cause of sudden death in at least half the patients who die of ischemic heart disease,[1] and may well be the most common in many other conditions. At one time ventricular fibrillation was regarded as always being terminal but it is now known both from experimental work[2] and clinical experience[3-6] that spontaneous recovery can occur particularly in patients with complete heart block.[7,8] If recognized early, means can be taken to correct this otherwise fatal arrhythmia.[9,10-13]

Ventricular fibrillation can be accidentally induced as in electric shock or during cardiac catheterization. There are also a number of drugs such as chloroform, cyclopropane, digitalis, adrenaline, acetylcholine, benzene, and veratrum alkaloids, which are fibrillatory agents. Potassium chloride and cooling can also produce ventricular fibrillation. Quinidine rarely causes accidentally induced ventricular fibrillation although it has been implicated in several cases.[14-18]

Quinidine is well recognized in the treatment of atrial fibrillation because of its ability to decrease myocardial excitability.[19-22] Thus, it is paradoxical that occasionally it can produce a serious arrhythmia, whereas in therapeutic amounts it is used in the management of arrhythmias.

Until recently, ventricular fibrillation has been treated by open thoracotomy, cardiac massage, and direct defibrillation[19] with increasing success. The pathology has usually been ascribed to coronary vascular disease although this need not be gross.[18-20] Many patients who die suddenly because of coronary occlusion have intact myocardiums at necropsy.[21] With the development of external cardiac massage,[22] and external defibrillation,[23] it is now possible to restore the rhythm and to resuscitate the patient by external means only.[24-26]

The purpose of this paper is to describe two patients who had very numerous attacks of ventricular flutter and ventricular fibrillation due to quinidine. Closed

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chest resuscitation and external defibrillation was completely successful in one patient. The other died some time after control of the arrhythmia.

Case reports

Case 1. V. L., a 31-year-old white woman, had developed valvular disease of the heart at the age of 6 years, after an attack of rheumatic fever. At school she did not take part in games, and when she was 17 she presented with subacute bacterial endocarditis and a soft, apical systolic murmur. She had three subsequent attacks of bacterial endocarditis all were proved by positive blood cultures and responded to therapy. Caesarean section was performed when she was 21 years old, and she was sterilized because of severe mitral incompetence. In December 1957 after the recurrence of rheumatic fever atrial fibrillation developed; with this, her effort tolerance diminished progressively so that admission for treatment of congestive cardiac failure was necessary. Surgical repair of gross mitral incompetence by means of an annuloplasty was performed as described elsewhere,[10] with an excellent immediate result. Within a fortnight of the operation, atrial fibrillation was restored to sinus rhythm with moderate doses of quinidine (30 grains in 10 hours), and she was discharged on a maintenance dose of 18 grains daily; digitalis was continued. A month after the operation, 5 days after quinidine was stopped, atrial fibrillation recurred and correction with quinidine again was successful. The maintenance dose was increased to 6 grains four times a day which was tolerated without symptoms. Sinus rhythm was maintained for 19 months after the operation, but during this period, signs of mitral incompetence gradually returned and increased. A gastrointestinal infection precipitated her into congestive cardiac failure with rapid atrial fibrillation. Hospitalization for control of the heart failure with digitalis and diuretics was once more necessary. She was then given our usual course of quinidine (6 grains every 2 hours, for 5 doses), with electrocardiographic control before each dose; this course was without success and without toxicity. The following day she received 9 grains every 2 hours for 5 doses; the last dose was given at 9 P.M. and again there was no clinical or undue electrocardiographic effect, and no signs of cinchonism. Three and a half hours later she suddenly collapsed and became pulseless, but recovered spontaneously. The electrocardiographic tracing showed atrial fibrillation runs of paroxysmal ventricular ectopic beats, and ventricular flutter. Half an hour later she developed a second Stokes-Adams attack; ventricular fibrillation was recorded. This was treated by external cardiac massage with a return of pulse and spontaneous restoration to atrial fibrillation. Thereafter at frequent intervals, numerous paroxysms of ventricular flutter and ventricular fibrillation occurred (Fig. 1). Syncope was always associated with ventricular fibrillation. During the ventricular flutter which generally preceded ventricular fibrillation, the patient was able to predict the onset of the Stokes-Adams attack. This gave sufficient time to prepare for cardiac massage. When the arrhythmia ceased, there was immediate return of consciousness. Molar lactate, 240 c.c., was infused intravenously with no appreciable effect. Continuous electrocardiographic monitoring recorded numerous attacks of ventricular flutter/fibrillation, which sometimes subsided spontaneously (Fig. 1) and sometimes required external cardiac massage before coordinated ventricular contraction was restored. After 8 hours a Morris internal defibrillator was attached and used externally. By this time the attacks of ventricular fibrillation had become more prolonged and were no longer reverted by external cardiac massage. Despite this the frequency of the attacks increased. Ventricular flutter became the dominant rhythm disturbance. As a desperate measure, procaine amide was administered: 100 milligrams was infused intravenously and repeated at 10-minute intervals for a total of 3 doses. Thereafter the attacks became much less frequent and were ultimately abolished. Hypotension developed and was initially controlled by an infusion of noradrenaline. The blood pressure, however, could not be maintained in spite of increased doses of noradrenaline, and consciousness was lost for the first time. Finally respiration was assisted by an endotracheal tube and a Bennet respirator. Cardiac standstill developed 28 hours after the first attack of ventricular fibrillation. In all, she had 50 attacks of ventricular flutter, 25 of alternating flutter fibrillation, and 15 of ventricular fibrillation; thus, a total of 90 episodes was recorded. Many more short attacks were not recorded.

At necropsy mitral valve disease (incompetence), left ventricular hypertrophy, and signs of chronic venous congestion were present. Histology showed that there were no active rheumatic lesions. There was slight myocardial and subendocardial fibrosis in the region of the mitral valve.

Case 2. H. M., a 28-year-old white woman, developed valvular disease of the heart at the age of 9 years, after an attack of rheumatic fever. At 21 a recurrence aggravated her condition and was followed by symptoms, although she was able to go through a normal pregnancy when she was 25. Atrial fibrillation probably developed shortly after the pregnancy, and her symptoms slowly progressed thereafter. Despite full cardiac therapy she became completely disabled from chronic heart failure.

The signs were those of gross mitral and tricuspid incompetence, atrial fibrillation, and congestive heart failure. Surgical repair of the mitral incompetence with a baffle was carried out on April 13, 1961, as described elsewhere.[10]

The initial response to the operation was excellent. The postoperative course was uneventful, and there was improvement in the mitral and tricuspid incompetence. Two weeks after the operation, after a test dose, 6 grains of quinidine was administered at 2-hour intervals for 5 doses in an attempt to correct the atrial fibrillation. Conversion to sinus rhythm did not occur nor were there any signs of toxicity clinically or electrocardiographically. On the following day, 9 grains every 2 hours for 5 doses were given again without effect.

Three hours after the last dose the patient complained of giddiness and nausea. She was found to be pale, shocked, and hypotensive. The electro-

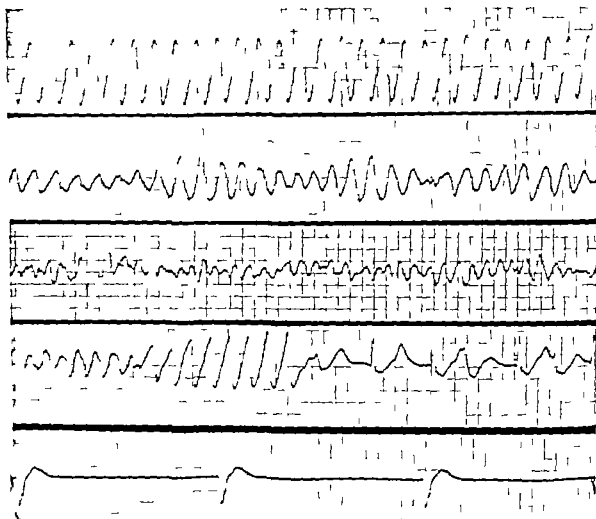


Fig. 1. The top tracing shows a paroxysm of ventricular flutter at 170 per minute. The second tracing shows ventricular flutter/fibrillation. The third shows ventricular fibrillation and the fourth shows spontaneous cessation of an attack of flutter fibrillation, atrial fibrillation with ventricular ectopic beats being restored. The fifth tracing was taken preterminally and shows atrial standstill with slow ventricular rhythm.

cardiogram showed marked quinidine effect with many aberrantly conducted beats or ventricular ectopic beats. Molar lactate, 120 c.c., was infused intravenously with apparent improvement and return of the blood pressure. Three hours later shock and hypotension recurred and the electrocardiogram showed atrial fibrillation with numerous ectopic beats and small paroxysms of ventricular tachycardia, indicative of extremely irritable ventricles (Fig. 2). Shortly thereafter she developed a Stokes-Adams attack which was treated by external cardiac massage and mouth-to-mouth breathing. An intravenous drip of 240 c.c. of molar lactate was begun immediately. The patient was completely conscious with no objective abnormality after the attack. Continuous electrocardiographic monitoring was instituted, and 3 hours later ventricular fibrillation recurred, associated with a Stokes-Adams attack. External cardiac massage was again successful in terminating the arrhythmia.

It soon became evident that the appearance of fairly regular ventricular ectopic beats heralded the onset of an attack. After the first few Stokes-Adams attacks, external cardiac massage could no longer terminate the arrhythmia so that external defibrillation with a Morris external defibrillator became necessary. The appearance of ventricular ectopic beats accurately predicted an impending attack of ventricular flutter or fibrillation, so that the resuscitation team could control each attack at its onset. Consciousness was lost shortly after the onset of flutter or fibrillation (Fig. 2). The patient herself was often able to anticipate an attack when she became aware of the ventricular ectopic beats. As soon as ventricular flutter or fibrillation began external cardiac massage was instituted and oxygen was administered by an anesthetist. If the attack did not subside immediately, external defibrillation was employed. During the succeeding 6 hours, three intramuscular injections of 10 c.c. of 20 per cent

magnesium sulfate 120 c.c. of molar lactate, 100 mg of intravenous hydrocortisone, and 1 Gm. of potassium chloride by slow intravenous drip were given without any apparent effect. It was found that small shocks merely controlled the individual attacks of ventricular fibrillation, but the attacks would then come on at more frequent intervals. With the application of shocks larger than necessary to control the immediate attack, the intervals between episodes of ventricular fibrillation became more prolonged. In all, 10 attacks of ventricular flutter 2 of flutter fibrillation, and 2 of fibrillation, totalling 14 attacks, were recorded, all associated with syncope. During each attack, coronary and cerebral circulation was adequately maintained by closed-chest massage, and the arrhythmia was terminated by electrical defibrillation. A pacemaker was never required. Fourteen hours after the onset, the paroxysmal arrhythmia disappeared and sinus rhythm was restored. Over the ensuing 18 hours, atrial fibrillation returned. No further attempts at correction were made. Postoperative recovery was satisfactory. Six months later she was remarkably well and was asymptomatic, living a full, normal life. There appeared to be no permanent damage produced by the recurrent episodes of ventricular fibrillation or by the defibrillation.

Discussion

These two patients are extraordinary because of the number of attacks of ventricular flutter and ventricular fibrillation that they had. There were at least 90 episodes in the first subject and at least 14 in the second. In both the arrhythmia was ultimately controlled.

Spontaneous defibrillation can occur in small animals and dogs,[9] but ventricular fibrillation is generally fatal in the higher mammals. Although rare spontaneous defibrillation has been encountered in man,[illegible] and occurred in both our patients on several occasions. As a rule however ventricular flutter and fibrillation are cardiac disturbances from which the heart seldom recovers on its own.

Until recently the accepted method of restoring the heart after cardiac standstill or fibrillation was to open the chest and massage the heart directly and then later defibrillate electrically if spontaneous recovery did not occur.[illegible] Thoracotomy however has been a most serious drawback since few physicians can embark on this procedure in a consulting room and most would think twice before doing it in the medical ward even though the practicality of this procedure has been reported.[illegible] The introduction of external defibrillation first by Zoll[illegible] and later by Kouwenhoven[illegible] in 1957 is obviously far more satisfactory than thoracotomy and cardiac massage if the apparatus is at hand. The problem

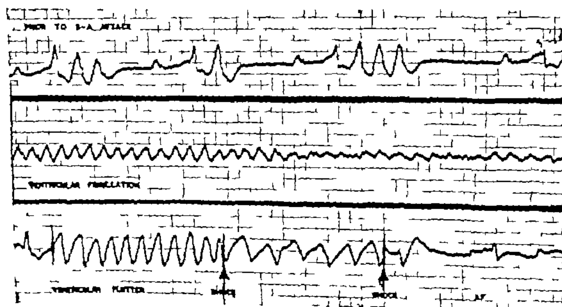


Fig. 2. The top tracing was taken just prior to the first Stokes-Adams attack and shows atrial fibrillation, right bundle branch block, and small paroxysms of ventricular tachycardia (flutter). The second tracing is extracted from a paroxysm of ventricular fibrillation. The third shows a paroxysm of ventricular flutter just after the onset. Two shocks were required to restore the basic rhythm (atrial fibrillation).

however is the maintenance of cerebral and coronary circulation until defibrillation can be carried out The heart will remain viable up to an hour but in order to function as a hydrostatic pump it must be adequately oxygenated[11,32] Defibrillation will be successful up to 3 to 4 minutes,[11] but if successful thereafter restoration of an adequate circulation with a normal blood pressure seldom occurs. Intracardiac injection of adrenaline or intra-arterial infusion of 5 per cent glucose and 1 to 2 milligrams of adrenaline[11] have been tried to restore the circulation

In June 1960 Kouwenhoven and associates,[33] from the Johns Hopkins Hospital published a method of closed-chest massage in man though apparently this method had been known experimentally to the Russians since 1945[32] This method will maintain an adequate circulation until electrical defibrillation can be instituted and adequate cardiac function restored The method is now frequently used with success[34,35,36] and has even been reviewed in the lay press.[36]

In regard to the patients reported on here the one died ultimately of cardiac standstill after prolonged hypotension but not of ventricular fibrillation and the other recovered completely External cardiac massage was easy to perform on both patients and immediately restored the pulse and circulation When the coronary blood supply is improved the heart stands a better chance of reverting spontaneously to normal rhythm Moreover the procedure allowed sufficient time for the necessary resuscitation equipment and staff to be assembled to deal with the situation. The external defibrillator was very effective in ending the arrhythmia and cardiac standstill was only momentary so that spontaneous ventricular function was soon restored The resuscitative procedures were so effective that even though our first patient had over 90 attacks and the second had more than 14 no cerebral or cardiac damage developed during the period of the arrhythmias.

Quinine was first used in cardiology by Wenckebach.[38] This was later replaced by quinidine as a more effective drug[37] Quinidine is used to prevent or abolish cardiac arrhythmias because of its ability to depress myocardial excitability[16,17] In spite of its wide range of usefulness, however it can be very toxic. Its toxicity is unpredictable and even though a careful watch is kept on plasma quinidine concentrations and regular electrocardiograms, toxicity may still occur Quinidine is used primarily in the treatment of patients with organic cardiac disease often severe and these patients are prone to unpredictable accidents even when quinidine is not given[17] Severe myocardial toxicity is manifested by frequent extrasystoles (or aberration) prolongation of the QRS and sinoatrial or complete A V block, ventricular tachycardia and ventricular fibrillation. Marked hypotension and cardiac standstill may also occur Routine electrocardiographic monitoring before each dose is generally advised but as is well demonstrated in our two patients, may be of no value at all in preventing toxic manifestations. In one of our patients the Stokes-Adams attack was the first manifestation of toxicity whereas in the other numerous ventricular ectopic beats appeared just before the first Stokes-Adams attack. Once the arrhythmia was established however continuous electrocardiographic monitoring was invaluable in treatment and control The onset of a fresh paroxysm of fibrillation could be accurately predicted by the appearance of ventricular ectopic beats, and appropriate measures applied

Ventricular tachycardia has been frequently reported as a manifestation of quinidine toxicity[14,15,21,36-42] although at the same time, quinidine is often the treatment of choice for this arrhythmia. The diagnosis of paroxysmal ventricular tachycardia must be made with great care,[43] however and cannot be substantiated unless evidence of atrial activity can be demonstrated either on the electrocardiogram or the phonocardiogram.[44] Quinidine is known to increase the conductivity of the A V node and for this reason digitalization is always recommended prior to treatment of atrial fibrillation with quinidine. The atrial rate is slowed conduction across the A V node increased and as a result, one-to-one conduction may occur At fast rates aberration is frequently present so that a one-to-one rhythm with bundle branch block appears (Fig 3) Nonethe-

less, authentic cases of paroxysmal ventricular tachycardia undoubtedly occur although probably far less frequently than the reports would indicate.

Sudden death as a result of quinidine therapy was reviewed by Thomson[#] in 1956. He noted that in the vast majority of cases in which necropsy was performed no cause for the sudden death could be found and thus, quinidine was implicated. Ventricular fibrillation due to quinidine may have been the cause of death but this has been reported in the literature with extreme rarity.

Kalmansohn and Sampson[44] in a foot note reported two cases of ventricular fibrillation which occurred during quinidine therapy in 1950. These cases occurred with low doses of the drug. A case each of ventricular fibrillation which occurred after quinidine was reported by Davis and Sprague[#] and by Acierno and Grubner.[#] In several other patients, ventricular fibrillation has been noted after quinidine but the drug could not be implicated solely since these patients had coronary heart disease[17] or heart block.[7,#,#] The infrequent reports of ventricular fibrillation due to quinidine therapy is surprising in that, experimentally, quinidine readily produces ventricular fibrillation in animals.[#-#] Ventricular fibrillation occurred in both our patients, and there are probably many more instances, but unless electrocardiograms are recorded at the time of death the arrhythmia will be missed. Ventricular fibrillation is probably the common cause of sudden death during quinidine therapy.

Treatment of quinidine toxicity[7] is primarily the cessation of the drug. The peak concentration of serum quinidine occurs 2 to 4 hours after a single oral dose. The disappearance from the serum follows an exponential decay curve and less than 10 per cent remains after 24 hours.[#] After repetitive doses approximately 40 per cent remains 12 hours after the last dose. Thus, it is apparent that simply tiding the patient over the first acute toxicity should be all that is necessary. With the metabolic detoxification of the drug recovery occurs rapidly. It is however the short period of severe toxicity that is the major problem. Marked toxic symptoms such as tinnitus and nausea can be treated with sedatives

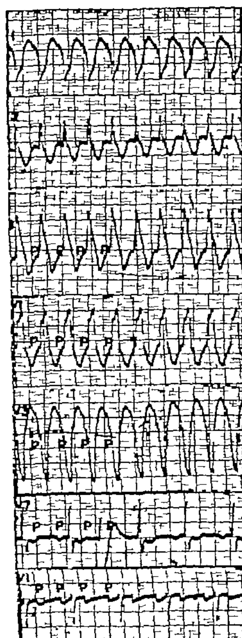


Fig. 3. At first glance, the rhythm disturbance appears to be paroxysmal ventricular tachycardia. However P waves can be detected in some of the leads at 190 per minute preceding each QRS complex. Quinidine has slowed the atrial rate, but when one-to-one conduction occurs, aberration with right bundle branch block develops. In the tracing second from the bottom, one-to-one conduction has spontaneously changed to two-to-one conduction; the ventricular rate is halved to 95 per minute. The third beat is one-to-one conducted, hence the aberration. The bottom tracing shows normal ventricular conduction with two-to-one block.

or antihistaminics and there is seldom any cause for alarm.

The severe cardiotoxic effects of quinidine are much more serious, and there is no specific antidotal agent that hastens the metabolic breakdown of the drug. A number of drugs have been tried in the treatment of quinidine toxicity. Adrenaline, noradrenaline, caffeine, acetylcholine, ephedrine and phenylephrine have all been tested experimentally.[44,46] Adrenaline and phenylephrine appear to be the most satisfactory especially as pressor agents. However, Bellet and associates[44] have shown that molar lactate can reverse the cardiotoxic and hypotensive effects of quinidine in dogs. This was observed repeatedly in their experiments. Apparently molar lactate decreases the concentration of quinidine, decreases serum potassium and shifts the pH to the alkaline side. Bailey[47] used molar lactate very successfully in two patients. In regard to the patients reported on here, each was given full doses of molar lactate with no appreciable decrease in the frequency of the attacks of ventricular fibrillation. Apart from the cardiotoxic effects of quinidine, the hypotension is also reported to be relieved by molar lactate[44]: a rise in blood pressure follows very closely an improvement in the electrocardiogram. However, this is less likely to occur when the toxicity is severe with prolonged and severe hypotension. In such cases, the response to adrenergic drugs is also poor.

In our first patient, hypotension developed after procaine amide. The hypotensive effects of this drug are well recognized.[44] These effects are most pronounced in patients with diseased hearts. Molar lactate, which acts in the same way as it does in quinidine toxicity, is advocated in the treatment of the hypotension produced by procaine amide.[33] It would seem that the progressive and subsequently irreversible hypotension this patient developed was due to a summation of effects due to procaine amide, quinidine, and a certain degree of cardiac and cerebral anoxia, which must have developed after so many attacks of ventricular fibrillation. It must be noted, however, that after procaine amide no additional attacks of ventricular fibrillation occurred.

In complete heart block, transient ventricular fibrillation or flutter is not an uncommon cause of syncope (Stokes-Adams attack) as has been well known for many years.[1,3,41] These attacks are self limited and usually tend to end spontaneously. They do not carry quite the same ominous prognosis as does ventricular fibrillation due to other causes. Quinidine and Pronestyl therapy is contraindicated in this condition,[9,41,49] but external defibrillation may be necessary. Ventricular fibrillation induced by quinidine has been reported in complete heart block, but, in view of the frequent association without this drug, care must be taken in attributing this arrhythmia to quinidine.

Summary

1. Two patients who had numerous repetitive attacks of paroxysmal ventricular flutter and fibrillation due to quinidine are reported upon.

2. The arrhythmia was controlled by external cardiac massage and external electrical defibrillation.

3. One patient survived after at least 14 paroxysms; the other died of cardiac standstill after over 90 paroxysms.

4. The treatment of ventricular fibrillation by external cardiac massage and defibrillation is discussed and reviewed.

5. The incidence of quinidine induced ventricular tachycardia and fibrillation is reviewed and the treatment discussed.

Addendum

Since this was written, we have encountered a third patient[51] who developed two Stokes-Adams attacks due to ventricular fibrillation induced by quinidine and terminated by external pummeling of the chest.

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REFERENCES

1. Bellet, S.: Clinical disorders of the heart beat, Philadelphia, 1953, Lea & Febiger, p. 219.
2. Brooks, C. McC., Hoffmann, B. F., Suckling, E. E., and Arias, O.: Excitability of the heart, New York, 1955, Grune & Stratton, Inc., p. 236.
3. Robinson, G. C., and Bredeck, J. F.: Ventricular fibrillation in man with cardiac recovery, Arch. Int. Med. 20:725, 1917.

4. Beck, C. S., Pritchard, W. H. and Feil, H. Ventricular fibrillation of long duration abolished by electric shock, J.A.M.A. 135:985 1947
5. Schwartz, S. P. Arloff, J., and Fox, C. Transient ventricular fibrillation, Am. Heart J. 37:21 1949
6. Perez Diaz, R., Echarabal, J. F., and Pernero, A. P.: Transient ventricular fibrillation. Complete recovery. Report of two cases, Rev. cubana cardiol. 19:121 1958. Cited from Excerpta Medica Cardiovas. Dis. 4:44, 1960.
7. Kerr, W. J. and Bender, W. L. Paroxysmal ventricular fibrillation and cardiac recovery in a case of auricular fibrillation with complete heart block while under quinidine sulphate therapy. Heart 9:269 1922
8. Parkinson, J. Papp, C., and Evans, W. The electrocardiogram of Stokes-Adams attack, Brit. Heart J. 3:171 1941
9. Schwartz, S. P. Margolis, M. P. and Firenze, A. Transient ventricular fibrillation. V. Effects of oral administration of quinidine sulphate on patients with transient ventricular fibrillation during established atrioventricular dissociation, Am. Heart J. 45:404, 1953.
10. Beck, C. S. Resuscitation for cardiac standstill and ventricular fibrillation during operation, Am. J. Surg. 54:273 1941
11. Hosler, R. M., and Wolfe, R. Closed chest resuscitation, A.M.A. Arch. Surg. 79:31 1959
12. Kouwenhoven, W. B. Milnor, W. R., Knickerbocker, G. G. and Chestnut, W. R. Closed chest defibrillation of the heart, Surgery 42 550 1957
13. Zoll, P. M. Leventhal, A. J. and Zarsky, L. R. N. Ventricular fibrillation. Treatment and prevention by external electric currents, New England J. Med. 262:105, 1960.
14. Bender, M. J. and Rosove, L. Paroxysmal ventricular tachycardia and fibrillation due to quinidine, Am. J. Med. 12:491 1952.
15. Acierno, L. J. and Gruboer, R. Utility and limitations of intravenous quinidine in arrhythmias, Am. Heart J. 41:733 1951
16. Lewis, T. Drury, A. N. Iliescu, C. L., and Wedd, A. M. Observations relating to the action of quinidine upon the dog's heart, with special reference to its action on clinical fibrillation of the auricles, Heart 9:55 1921
17. Sokolow, M. and Perloff, D. The clinical pharmacology and use of quinidine in heart disease. Prog. Cardiovas. Dis. 3:316, 1961
18. Robert, E. L. Resuscitation from ventricular fibrillation complicating acute coronary occlusion, Am. J. Cardiol. 7 724, 1961.
19. Celio, A. Cardiac arrest with coronary occlusion, J. Internat. Coll. Surg. 25:299 1956.
20. Beck, C. S., Wilkinson, E. C., and Barry, F. M. Fatal heart attack and successful defibrillation, J.A.M.A. 161:434, 1956.
21. Adelson, L., and Hoffman, W.: Sudden death from coronary occlusion, J.A.M.A. 176 129 1961
22. Kouwenhoven, W. B. Jude, J. R., and Knickerbocker, G. G.: Closed chest cardiac massage, J.A.M.A. 173 1064 1960
23. Zoll, P. M. Paul, M. H. Leventhal, A. J., Harmel, L. R., and Gibson, W.: The effect of external electric currents on the heart, Circulation 14:745 1956.
24. Thal, F. J. Closed chest cardiac resuscitation in acute myocardial infarction, Am. J. Cardiol. 7:731, 1961
25. Goldberg, T. H. and Palman, R. S. Therapy of Stokes-Adams syndrome. Am. J. Cardiol. 5: 540, 1960
26. Baringer, J. R., Salzman, E. W. Jones, W. A., and Friedlich, A. L. External cardiac massage, New England J. Med. 265:62, 1961
27. Barnard, C. N. McKenzie, M. B., and Schrire, V. A surgical approach to mitral insufficiency Brit. J. Surg. 47:655 1961
28. Barnard, C. N. and Schrire, V. Surgery of mitral incompetence, Postgrad. M. J. 37:666, 1961.
29. Lewis, T. Drury, A. N. Wedd, A. M. and Iliescu, C. L. Observations upon the action of certain drugs upon fibrillation of the auricles Heart 9:207 1922.
30. Mozen, H. E., Katzman, R., and Martin, J. W. Successful defibrillation of the heart. Resuscitative procedure started in medical ward and completed in operating room. J.A.M.A. 162 111 1956.
31. Zoll, P. M. Resuscitation of the heart in ventricular standstill by external electric stimulation, New England J. Med. 247 768, 1952.
32. Hosler, R. M. Cardiac excitability and resuscitation, Am. J. Cardiol. 6:994 1960.
33. Hosler, R. M. Present-day cardiac resuscitation, Am. J. Cardiol. 8:297 1961.
34. Morgan, R. R. Laceration of the liver from closed-chest cardiac massage, New England J. Med. 265:82, 1961
35. Kearney, P. If a heart stops beating—there's help at hand, Reader's Digest 78:47 1961
36. Wenckebach, H. F. and Winterberg, H. Die unregelmässige Herztätigkeit und ihre klinische Bedeutung, Leipzig and Berlin, 1927 W. Engelmann. Cited by Friedberg,[37] p. 365
37. Friedberg, C. K. Diseases of the heart, ed. 2 Philadelphia 1956, W. B. Saunders Company
38. Sokolow, M. and Edgar, A. L. Blood quinidine concentrations as guide in the treatment of cardiac arrhythmias, Circulation 1:576, 1950.
39. Levy, R. L. The clinical toxicity of quinidine, J.A.M.A. 78 1919 1922 Levy, R. L. Clinical studies of quinidine, Arch. Int. Med. 30:431 1922.
40. Hepburn, J. H. and Rykert, H. E. The use of quinidine sulphate intravenously in ventricular tachycardia, Am. Heart J. 14:620, 1937
41. Williams, C., and Ellis, L. Ventricular tachycardia: an analysis of thirty-six cases, Arch. Int. Med. 71 137 1943
42. Armbrust, C. A., Jr. and Levine, S. A. Paroxysmal ventricular tachycardia. A study of one hundred and seven cases, Circulation 1:28 1950
43. Allmurung, M. M., and Chua Chiaco, M. Aberrant ventricular conduction simulating paroxysmal ventricular tachycardia during quinidine therapy Am. Heart J. 52:462, 1956
44. Schrire, V., and Vogelpoel, L.: Clinical and

electrocardiographic differentiation of supra ventricular and ventricular tachycardia with regular rhythm Am. Heart J 49:162 1955

45 Thomson, G W Quinidine as a cause of sudden death Circulation 14:757 1956

46. Kalmansohn, R W and Sampson J J Studies of plasma quinidine content. II Relation to toxic manifestations and therapeutic effect Circulation 1:569 1950

47 Rakov H L. Ventricular fibrillation in acute coronary artery thrombosis during intravenous administration of quinidine sulphate report of a fatal case, Ann Int. Med 16:571 1942

48. Davis D and Sprague H B Ventricular fibrillation its relation to heart block, Am. Heart J 4:559 1928.

49 Schwartz, S. P and Jezer A. The action of quinine and quinidine on patients with transient ventricular fibrillation, Am Heart J 9 792 1934

50. Drury A N Horsfall, W N and Munley W. C. Observations relating to the action of *quinidine upon the dog's heart the refractory* period of and conduction in ventricular muscle, Heart 9:365 1922

51 Wégria, R. and Nickerson, N D Effect of papaverine epinephrine and quinidine on fibrillation threshold of mammalian ventricles, J Pharmacol. & Exper Therap. 75:50, 1942

52. Mileh E., Zindahl, W T., Egan, R. W Hess T W Anderson, A., and David J Experimental prevention of sudden death from acute coronary occlusion in the dog, Am Heart J 50:483 1955

53 Brown, M G Holzman D and Creedman, E. Serum quinidine concentration in congestive heart failure, Am J M Sc. 225:129 1953

54 Finnegan T R. L. and Lawrence, J R. Depression of the heart by quinidine and its treatment, Brit. Heart J 16:341 1954

55 Weisman, S A. A study of the analeptic value of certain drugs in the treatment of quinidine depression, Am. Heart J 21:240 1942.

56. Bellet S., Hamdan G Somlyo, A., and Lara, R. A reversal of the cardiotoxic effects of quinidine by molar sodium lactate an experimental study Am. J M Sc. 237:165 1959

57 Bailey D J Jr Cardiotoxic effects of quinidine and their treatment, Arch Int. Med 105: 13 1960.

58. Kersman, J M McClendon, R. L., and Hansen, W R. Procaine amide (Pronestyl) in the treatment of cardiac arrhythmias, Am J M. Sc. 222:375 1951

59 Bellet, S., Hamdan G Somlyo A., and Lara, R. A reversal of the cardiotoxic effects of procaine amide by molar sodium lactate, Am. J M Sc 237 177 1959

60 Robbin, S. R Goldfein, S., Schwartz, M. J and Dack, S Adams-Stokes syndrome. The treatment of ventricular asystole, ventricular tachycardia and ventricular fibrillation associated with complete heart block, Am. J Med 18:577 1955

61 Harwood-Nash, D C. Ventricular fibrillation due to quinidine therapy South African M J (In press)

The complex pattern of response to coumarin drug therapy

The inadequacy of the prothrombin test as a guide to hypocoagulability

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Coumarin drugs, such as Dicumarol and Coumadin, are widely used in the treatment of occlusive vascular and thromboembolic diseases. They are a mainstay of therapy in myocardial infarction. The use of the one-stage prothrombin test as a guide to dosage is almost universal. The desired therapeutic range is usually a prothrombin time between 20 and 30 per cent of "normal."

Three fundamental concepts form the basis of these practices: coumarin drugs are prothrombinopenic; the degree of hypocoagulability produced is directly related to the degree of hypoprothrombinemia; and the "prothrombin time" test adequately assays the changes in the coagulation system.

The reluctance of some physicians to employ this mode of therapy stems, in part, from recognized difficulties in its use. These may be summarized as follows: (1) unexplained bleeding at "safe" levels of prothrombin; (2) unexplained thromboembolism at "safe" levels of prothrombin; and (3) unexplained lack of bleeding when occasionally a patient is inadvertently brought to very low prothrombin levels.

Consideration of these phenomena reveals that a subtle confusion has beclouded the problem. The difficulties do not provide a basis for questioning the value of anticoagulant therapy, but rather for questioning the relationship between the one-stage prothrombin test results and the degree of hypocoagulability achieved. In the past several years, a body of evidence has been produced which provides further support for questioning or doubting that the one-stage prothrombin test adequately reflects the degree of hypocoagulability. Thus it has been shown[2-4] that at least three other coagulation factors in addition to prothrombin are depressed by the coumarin drugs: factor IX (Christmas factor, PTC), lack of which occurs in hemophilia B; factor VII (proconvertin, SPCA);[7] and factor X (Stuart factor).[8] The depression of factors IX and X is of particular significance inasmuch as they function in the earliest stage of coagulation—thromboplastin generation. Impaired thromboplastin generation is not reflected in the prothrombin time test.

It is the purpose of this paper to describe the complexity of response to coumarin drugs. This is characterized by the independent variation in rate and degree of

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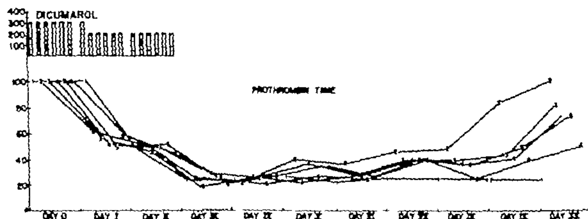


Fig. 1A. One-stage prothrombin results. Depression of prothrombin time of 6 normal subjects given Dicumarol. Note uniform responses.

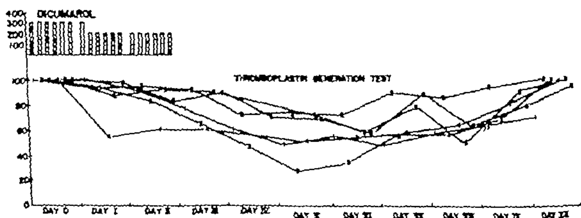


Fig. 1B. Thromboplastin generation test results. Variable depression in time, rate and degree of thromboplastin generation in subjects with same prothrombin depression curves (see Fig. 1A).

several factors of coagulation. In our experience the resultant pattern renders the prothrombin time test misleading as an index of the degree of hypocoagulability produced and inadequate as a guide to the dosage of the drug to be employed.

Materials and methods

1. Collection of blood. Blood was received into a siliconized syringe after clean venipuncture, collected in a siliconized test tube containing one-ninth volume of 3.8 sodium citrate solution, and centrifuged for 10 minutes at full speed in an International table-top angle-head centrifuge. The plasma, separated by siliconized Pasteur pipettes, was collected in siliconized glass test tubes and refrigerated or frozen at −15 to −12 degrees Fahrenheit until used in the appropriate tests indicated below.

2. Tests. The tests included (a) thromboplastin generation,[9] (b) one-stage prothrombin time,[10] employing thromboplastin from the human brain,[11,12] (c) factor VII,[14] and (d) the Stuart factor.[13]

Results

Typical responses to coumarin drug therapy are shown in Figs. 1A through 1D. The subjects were normal healthy medical students. The graphs have been arranged in a comparable time sequence for ease of examination. Fig. 1A shows the one-stage prothrombin depression. Dosage of the drug was based on one-stage prothrombin results. As may be seen, there was a rapid and satisfactory lowering of the one-stage prothrombin results to the desired clinical range. Thereafter the drug was discontinued and the patient's values returned toward normal. The in-

formation contained in Fig 1*A* represents the total information usually available to the clinician in regard to the coagulation status of his patient. It is widely assumed that such a curve reflects not only the one-stage prothrombin results but also the degree of hypocoagulability achieved Fig 1*B* shows the effect of the coumarin drug on the first stage of blood coagulation, represented here in the form of the thromboplastin generation test. Several things are noteworthy in this group There was, in general, a lag before the thromboplastin generation was depressed. The level of depression varied from patient to patient. There was no correlation between the rate or level of depression of thromboplastin generation and the prothrombin time. Depression of thromboplastin generation has only rarely been observed to be greater than that of prothrombin. Figs. 1*C* and 1*D* show the reduction of factor VII and the Stuart factor in the same volunteers. Although depression of these two factors does not have the same importance in producing hypocoagulability as does the depression of factors measured by the prothrombin test and the thromboplastin generation test, they are sensitive indicators of the action of coumarin drugs.

Fig 2 shows the results in a single patient of long term continuous anticoagulant therapy for coronary artery disease. While on this mode of therapy in the 2 year period after discharge from the hospital the patient repeatedly manifested clinical evidence of "little strokes" (Al

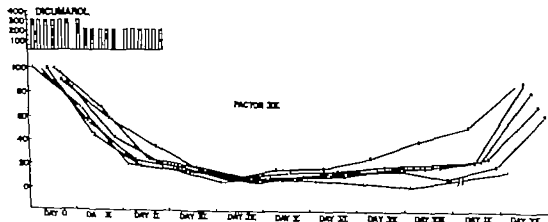


Fig 1*C* Factor VII results. Uniform depression of factor VII (Same subjects as Fig 1*A*)

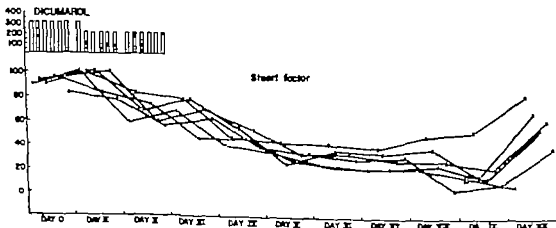


Fig 1*D* Stuart factor results. Depression of Stuart factor during administration of Dicumarol. (Same subjects as Fig. 1*A*)

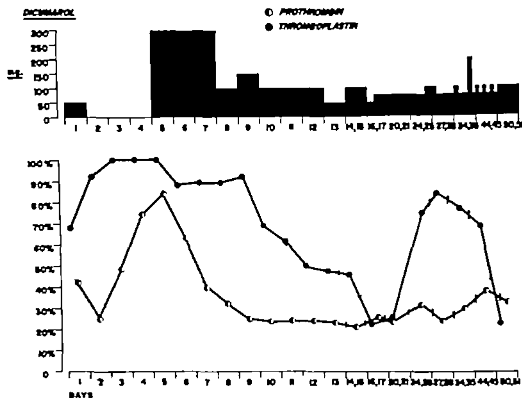


Fig 2 Thromboplastin generation escape in a case of Alvarez's disease. Comparison of the depression of the initial stage of coagulation (thromboplastin generation) with the depression of the latter stages of coagulation (prothrombin time) in a patient with Alvarez's disease. Note *the independent course of the thromboplastin generation test relative to prothrombin time, and* the escape of the former on the twenty fourth day

varez's disease) It can be seen that the one-stage prothrombin results responded rapidly both to the withdrawal and administration of Dicumarol and were maintained *at a clinically satisfactory level* Fig 2 shows other effects of the coumarin drug on the patient's coagulation system. Thromboplastin generation lagged behind and was far more variable than the prothrombin level At one point (on the twenty-fourth day) when the prothrombin rose briefly to 32 per cent, the thromboplastin generation escaped almost to normal levels.

Figs. 3*A* and 3*B* show the results of coagulation in another patient a physician on long term anticoagulant therapy after myocardial infarction Fig 3*A* indicates the attainment and maintenance of a satisfactory" prothrombin level upon administration of Dicumarol It may be seen that this level was maintained for approximately 2 weeks before the patient manifested hematuria The figure also indicates the thromboplastin generation results (in per cent of normal) the variable trend of thromboplastin generation is evident. Hematuria was manifested at *the point of greatest depression of thromboplastin* generation. Fig 3*B* gives the levels of factors VII and X At the time of hematuria factor X reached a level of 0 per cent. Administration of Dicumarol was discontinued and the patient was allowed to return to normal levels of all coagulation factors. *He was then started* on a regimen of Coumadin. The results are shown in Figs. 3*C* and 3*D*

Fig 3*C* demonstrates the prothrombin and thromboplastin generation results, which are quite similar to those obtained with Dicumarol Again after a prolonged maintenance of the patient's one-stage prothrombin results in a safe range hematuria was manifested At this time (Fig 3*D*) the Stuart factor showed 0 per cent Anticoagulant therapy was discontinued because of the complication pro-

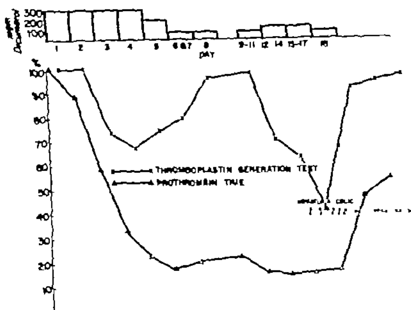


Fig. 3A Hematuria during anticoagulant therapy correlation with thromboplastin generation test. The response curves of the thromboplastin generation test and prothrombin time in a case of hematuria associated with administration of Dicumarol. Note the nonparallel course of the two curves, and the manifestation of hematuria at the point of greatest depression of the thromboplastin generation test.

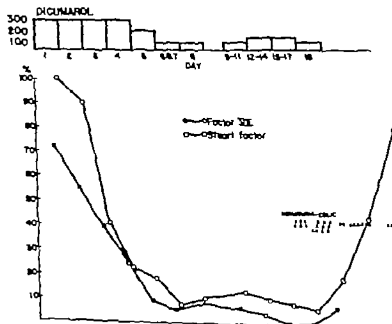


Fig. 3B Hematuria during anticoagulant therapy; correlation with Stuart factor results. Same patient as in Fig. 3A. Not Stuart factor t zero per cent coincident with manifestation of hematuria.

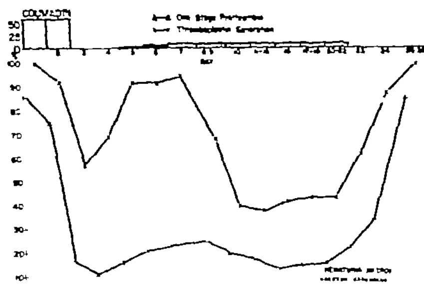


Fig. 3C. Hematuria during anticoagulant therapy. Same patient as in Figs. 3A and 3B but on Coumadin therapy. Note striking similarity of coagulation response and hematuria as with Dicumarol.

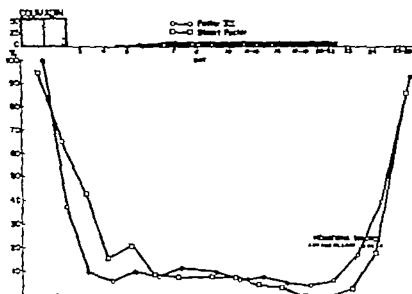


Fig. 3D. Hematuria during anticoagulant therapy: correlation with Stuart factor results. Same patient as in Fig. 3C, on Coumadin therapy, shows same pattern of response of coagulation and its relation to hematuria as with Dicumarol.

duced and the undesirable effect of the anxiety generated. It is obvious with both Dicumarol and Coumadin that neither thromboplastin generation nor the level of the Stuart factor could have been suspected from the prothrombin test results.

The results in another patient on long term Dicumarol therapy for coronary artery disease are shown in Fig. 4. Some years before her initial cardiac manifestations, the patient had had among other things a bilateral oophorectomy. Her clinical course was marked by progressive intractable coronary artery disease which did not respond to any of the usual forms of treatment.

Fig 4A shows two things which are of immediate interest the patient's prothrombin time was shorter than normal and by extrapolation of the normal curve her "prothrombin level was above normal Very large doses of the drug were required to reduce and maintain the desired prothrombin level. It will be noted that after the thirty-fifth day the one-stage prothrombin level was brought to values below those usually considered adequate. Fig 4A shows other coagulation effects of the drug The patient's first stage of coagulation, reflected in the thromboplastin generation test remained normal for some 30 days, even on very large doses of Dicumarol Because of the patient's symptoms the aim of therapy at that time was to decrease the coagulability in both the first and latter stages of the coagulation process. At this time, therefore, the dosage of the drug was increased with a resultant slow drift of the one-stage prothrombin time to approximately 10 per cent of normal. *Depression of thromboplastin generation* to the high twenties per cent of normal was achieved This condition was maintained for approximately 1 week. At that time the patient noticed melena, which she did not report

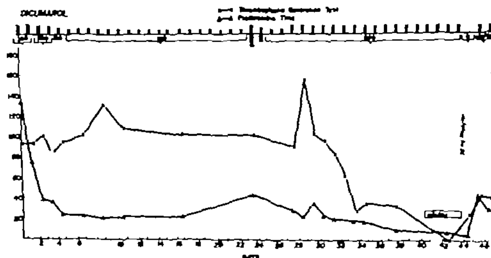


Fig 4A Melena during anticoagulant therapy correlation with thromboplastin generation test. Comparison of the responses of the thromboplastin generation test and the prothrombin time test in a case of intractable progressive coronary artery disease Note the initial supernormal prothrombin time, the high doses necessary to maintain the usual "therapeutic range," the lack of depression of the thromboplastin generation test with long-term prodigious doses of Dicumarol, and the manifestation of melena at the low point of the thromboplastin generation test curve.

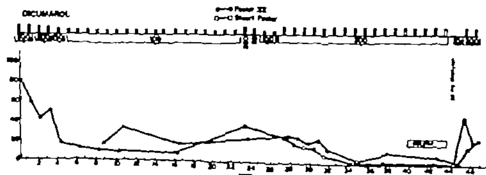


Fig 4B Melena during anticoagulant therapy Same patient as in Fig 4A Note low values of factor VII and Stuart factor associated with melena.

to her physician in spite of specific instructions. During this time thromboplastin generation fell to very low levels. Indeed, the forty-second day represents one of the rare occasions when we have observed a depression of thromboplastin generation greater than that of prothrombin. Shortly thereafter, the patient was hospitalized because of severe symptoms. The existence of melena was immediately discovered and the patient was given 50 mg. of Mephyton intravenously, as noted in the figure. There was an immediate return toward normal of the thromboplastin generation and the prothrombin levels. However, the patient soon died. At postmortem examination coronary atherosclerosis with almost complete obliteration of the lumina throughout the myocardium was seen. This finding was related to the interesting although controversial possible relationship between atherogenesis and the normal state of the patient after bilateral oophorectomy. Fig. 4B shows the results of analyses of factors VII and X in this patient. In general, their depression was rapid and maintained at a low level throughout. Analysis of factor VII showed a depression to levels of 0 per cent from the thirty-fifth to the forty-fourth day. At that time factors VII and X showed a return toward normal coincident with the administration of Mephyton intravenously.

Discussion

The data presented in this paper deal with the variability and complexity of the response of coagulation to coumarin drugs.

Fig. 1 shows the effects in a volunteer group of normal subjects undergoing acute short-term therapy. Figs. 2 through 4 have to do with patients on long-term anticoagulant therapy. Two types of coagulation tests have been employed. One type attempts to measure portions of the coagulation schema. Thus, the thromboplastin test assays the first stage of coagulation and the prothrombin time test measures the latter two stages of coagulation. These tests show the varied responses of the several stages to coumarin drug therapy. It is important to note that the rate and degree of depression of the first stage of coagulation is not necessarily parallel or similar to that of the latter stages of coagulation. Therefore, the same patient may have different levels of thromboplastin generation with the same prothrombin time, and patients under anticoagulant therapy can have coincident levels of prothrombin with markedly different levels of thromboplastin generation. Thromboplastin generation reflects an important stage of blood coagulation—the initial stage. Its depression may be as important in the production of hypocoagulability as is the depression of the factors measured by the one-stage prothrombin test.

The second type of test employed in this study shows depression of single factors, e.g., factor VII and factor X. Although their reduction per se may have a minor effect in producing hypocoagulability, they appear to be sensitive indicators of response and more subtle indices of the progression of events than can be obtained from the cruder and more significant tests, such as thromboplastin generation and one-stage prothrombin time.

The administration of coumarin drugs to human beings has been shown to produce a complex pattern of results. At least four separate and distinct coagulation factors are variously depressed during the course of therapy. Reduction of each factor contributed in its own particular way toward the desired state of hypocoagulability. It is essential to recognize that the coumarin drugs produce a type of acquired hemophilia. The degree of the hemophilic effect and the rate of its production cannot be inferred from the one-stage prothrombin results. The situation is not dissimilar to the discovery by a physician that his patient recently initiated on an anticoagulant regimen has hemophilia of unknown severity. It seems gratuitous to emphasize in this situation that the one-stage prothrombin results would not be considered adequate as a measure of the hypocoagulability of the patient.

This situation has been recognized by Owren[11] and practical attempts to fashion a single test which reflects over-all hypocoagulability have led to the use of the thrombotest reagent.[4] This test is said

to assay the depression of all four factors which are depressed during coumarin therapy In particular it is said to be highly sensitive to depression of factors IX and X below 15 and 10 per cent re spectively As an alternative, one could employ the thromboplastin generation test and the one-stage prothrombin test to assess the effects of drug action It is our present belief that unless there is a substantial reduction in the first stage of coagulation, the degree of hypocoagulability achieved is inadequate. The desirable level of depression of the thromboplastin generation and the one-stage prothrombin test for optimal clinical results have yet to be adequately investigated

REFERENCES

1 Sise, S. H Kimball, D M and Adams, D Plasma thromboplastin component (PTC) deficiency produced by prolonged administrations of prothrombopenic anticoagulants, Proc. Soc. Exper Biol. & Med. 89:81, 1955
2. Johnson, S. A., and Seegers, W H The re duction of autoprothrombin II activity with Dicumarol, Circulation Res. 4 182, 1956.
3. Verstraete, M The complexity of the Dicumarol effect, Arch. internat. pharmacodyn. 123:31 1960.
4. Owren, P A Thrombotest new method for controlling anticoagulant therapy Lancet 2 754, 1959
5. Aggeler P M., White, S G., Glendening, M B Page, E W Leake, T B and Bates, G. Plasma thromboplastin component (PTC) deficiency a new disease resembling hemophilia, Proc Soc. Exper Biol & Med. 79:692 1952.
6. Alexander B Goldstein, R., and Landwehr G. The prothrombin conversion accelerator of serum (SPCA) its partial purification and its properties compared with serum Ac-globulin, J Clin. Invest. 29:881 1950.
7 Owren, P A. Proconvertin, the new clotting factor (Letter to the Editor) Scandinav J Clin. & Lab Invest. 3 168, 1951
8. Hougie, C., Barrow E., and Graham, J Stuart clotting defect, J Clin. Invest. 36:485, 1957
9 Biggs, R., and MacFarlane, R. G. Human blood coagulation and its disorders, Springfield, Ill., 1957 Charles C Thomas, Publisher Vol. 2, p. 401
10 Tocantins, L M The coagulation of blood. Methods of study New York, 1955, Grune & Stratton, Inc
11. Gollub, S., Kaplan, F E., and Meranze, D R. Qualitative difference between brain and lung thromboplastic suspensions, Am. J Physiol. 162:2, 1950.
12. Gollub, S Kaplan, F E., and Meranze, D R. Thromboplastic potency changes A result of bacterial action, Proc. Soc. Exper Biol. & Med. 73 725 1950.
13 Bachmann, F Duckert, F., and Koller F The Stuart Prower factor assay and its clinical significance, Thromb Diath. Haemorrh. 2 1 1958.
14 Owren, P A. The laboratory and social organization of anticoagulant treatment of large groups of patients, Proceedings of the Seventh European Congress of the Society of Hematology London, 1959 Part II, 1960, p 603.

The incidence of myocardial infarction and the mortality in surviving patients*

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In our clinic a total of 13,350 patients including 6 678 men and 6,672 women were treated between 1948 and 1960 During this time there were 520 patients with myocardial infarction i.e. 3 9 per cent of the total number treated

Since the criteria for the clinical diagnosis of myocardial infarction during the time of observation have changed we are giving them here

The average period of hospitalization for each patient except those who died was 4 to 6 weeks. The diagnoses were usually based on a consideration of the history physical examination laboratory data and clinical course

The cardiac pain was judged not only by its long duration but also by its severity and failure to be relieved by nitroglycerin An electrocardiogram was recorded in all patients (5 leads until 1955 and 12 leads after that) Distinctive electrocardiographic changes in the many successive tracings could determine the diagnosis. Also very helpful in determining the diagnosis were shock pulmonary edema fever leukocytosis increased rate of sedimentation and since 1958 serum transaminase activity

However in some cases it was difficult to make a diagnosis particularly when the clinical syndrome was atypical Only very careful clinical study with several repetitions of laboratory tests would permit an adequate diagnosis. Our diagnoses in the patients who died were confirmed by autopsy in 90 per cent of the cases.

Over this period of 12 years we have observed that in the clinic the number of patients annually with a diagnosis of myocardial infarction has increased to such an extent that in the tenth year of observation the number was almost tripled from 20 patients annually to 57 This might have been connected with the particular interests of the clinic, but it should also be borne in mind that patients are admitted only on certain days and that within the last 6 years two new departments for internal diseases have been opened in Cracow

A rise in the incidence of myocardial infarction and mortality due to it has been observed in many other countries.[8,14,16]

As in many other countries,[8,21,22,24,25] a smaller incidence of myocardial infarction in women than in men has also been observed in Cracow In 12 years, we have had no instance of any woman under 40 years of age with myocardial infarction.

As Fig 1 shows out of a total of 520 patients with myocardial infarction only 88 were women so that the ratio of women

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Table I

Period	*Men*	*Women*	*Ratio of incidence*	*Per cent women*
1948–51	125	21	1:5.95	14 4
1952–55	128	26	1 4.92	16.9
1956–60	179	41	1 4.36	18.7
Total	432	88	1 4.9	16.9

to men was 1 4.9 In our observations, myocardial infarction appeared in women only after the age of 40 and its frequency rose parallel to age. After the age of 70 the ratio of incidence in women and men fell to about 1.2.6. The last proportion may be a consequence of the fact that in Poland 30 per cent fewer men than women live to be over 70 years of age.[18]

A more accurate analysis of our clinical material with reference to the difference of incidence in the two sexes has given us data for successive 4-year periods (shown in Table I)

From Table I we see that the total incidence of cardiac infarction according to our observations, has recently risen proportionately more among women than among men. It must be noted however that it is possible to affirm this with a degree of probability equal to only 70 per cent.

Taking into account the investigations of Dock[4] and Lober[22] on the causes of the more frequent occurrence of myocardial infarction in men, and bearing in mind the lower blood serum turbidity which we have found in healthy women under the age of 50[20] we have grounds for assuming that in younger women factors predominate which clear the blood serum and that these may give them protection against the occurrence of myocardial infarction.

The peak incidence of myocardial infarction in our patients occurs both in women and in men between 50 and 60 years of age. Of all our patients 40 7 per cent are included in this age group. In the fifth decade the figure mentioned falls to 27 1 per cent, and in the seventh to 23 4 per cent. It follows from this that myocardial infarction occurs between 40 and 70 years of age in 91.2 per cent of the patients. These figures are, on the whole, in agreement with those given in the literature.[9,22,23]

The patients were from the three employment groups (1) mental workers (2) craftsmen and (3) physical laborers (doing heavy work) All were active in their respective occupations. Table II shows the proportions in Cracow of these three occupation groups.*

After calculating the "t" test, we find that the correlations in Table II are statistically significant. A significance ($t > 3$) exists between all of them. We find the greatest number of cases of myocardial infarction among the mental workers, and the next greatest number among craftsmen. Rather striking is the fact that by far the smallest number of cases of myocardial infarction was found among physical workers who were doing heavy labor

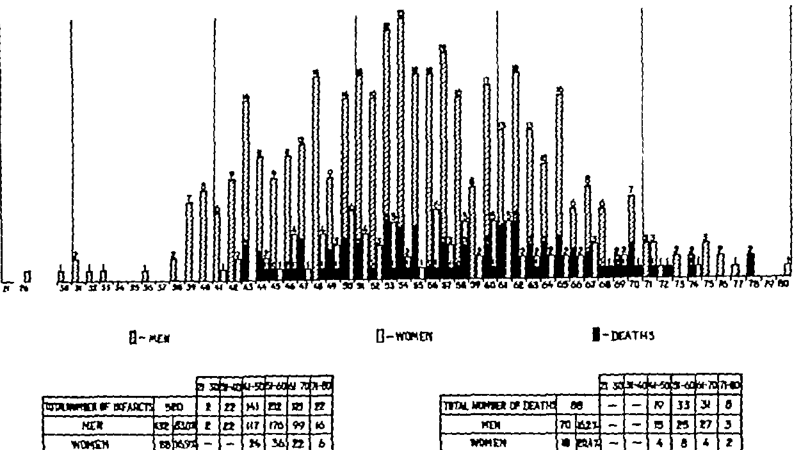
Among the diseases which precede myocardial infarction, hypertension should be mentioned in first place. In our group of patients hypertension was found in 54 per cent of the women and 30 per cent of the men. This observation indicates that hypertension in patients with myocardial infarction is at least three times as frequent as it is, on the average, in the same general population.[19]

In the group of patients with myocardial infarction under discussion, we found diabetes in 14 patients of these, 13 died while under observation These data confirm the view that concurrent diabetes makes the prognosis of length of survival markedly worse in patients with myocardial infarction.

Out of the group of 520 patients in the clinic, 88 (16.9 per cent) died. Postmortem examinations were performed in 83 of these (most in the Department of Pathological Anatomy Cracow Academy of Medicine—Director Professor J Kowalczykowa, M.D 5 in the Cracow Department of Forensic Medicine—Director Professor J Olbrycht, M D and 1 in the Prosectorium of the Military Hospital—Dr S. Stefanko)

At postmortem examination the clinical diagnosis of infarction was confirmed in

*These numbers are taken from [illegible]



			21-30	31-40	41-50	51-60	61-70	71-80
TOTAL NUMBER OF INFARCTS	520		2	22	141	[illegible]	[illegible]	22
MEN	432	83.08	2	22	117	170	99	16
WOMEN	88	16.92	—	—	24	36	22	6

			21-30	31-40	41-50	51-60	61-70	71-80
TOTAL NUMBER OF DEATHS	88		—	—	19	33	31	8
MEN	70	16.23	—	—	15	25	27	3
WOMEN	18	[illegible]	—	—	4	8	4	2

Fig. 1. Graph of patients with cardiac infarction treated in Medical Clinic I from 1948 to April 30, 1960.

73 cases (90.3 per cent) which agrees with the observations of Friedberg and associates.[9] Except for 1 patient with thrombosis a greater or lesser degree of disseminated vascular atherosclerosis was found in all cases. From the results of anatomicopathologic examinations now given and from the investigations of other authors,[4,7,13,14,15,17,21] it seems beyond controversy that the basis of myocardial infarction is almost always atherosclerosis of the coronary arteries and that other causes are rare exceptions.

By way of illustrating the difficulties of diagnosis in 8 patients in whom cardiac infarction was not confirmed post mortem we present in brief form the anatomicopathologic findings. (1) Male, aged 51. Disseminated arteriosclerosis, especially of the aorta and syphilitic meso-aortitis. Rupture of the supravalvular part of the aorta after dissecting hematomatas and rupture into the pericardial sac. (2) Female aged 49. Thrombophlebitis of the small saphenous vein subsequent to emboli in a pulmonary artery. Hemorrhagic infarct of the left inferior pulmonary lobe. Very pronounced dilation of the whole heart, and cardiac lipomatosis. Foramen ovale open. (3) Female, aged 48. Disseminated arteriosclerosis. Cerebral hemorrhage in the region of the lateral ventricle in the left hemisphere. Subarachnoidal hemorrhage at base of brain. Dilation of the whole heart. Hydropericardium. Cicatrices after splenic infarct. (4) Female aged 68. Disseminated arteriosclerosis, especially of the basal cerebral and coronary arteries. Dilation of the whole heart. Carcinoma of the stomach. (5) Male aged 53. Advanced disseminated arteriosclerosis, especially of the coronary arteries. Sudden death. (6) Male aged 60. Moderate disseminated arteriosclerosis especially of the coronary arteries. Fibrinous hemorrhagic pericarditis. Hypertrophy and dilation of the whole heart. Spontaneous rupture of the spleen as a sequel to hemorrhage into the peritoneal cavity. Generalized anemia. (7) Male aged 61. Disseminated arteriosclerosis. Advanced degree of hypertrophy of the whole heart but most pronounced in the left side of the heart. Very large dissecting aneurysm of the whole of the descending aorta. Aneurysmal rupture and very large hematoma of the mediastinum retroperitoneal. Hemothorax, especially on right. (8) Male aged 53. Moderate disseminated arteriosclerosis. Pulmonary emphysema. Dilation of the whole heart. Pulmonary edema. Previous cholecystectomy. Sudden death.

The acute symptoms of coronary insufficiency in this group of patients caused difficulties in diagnosis.

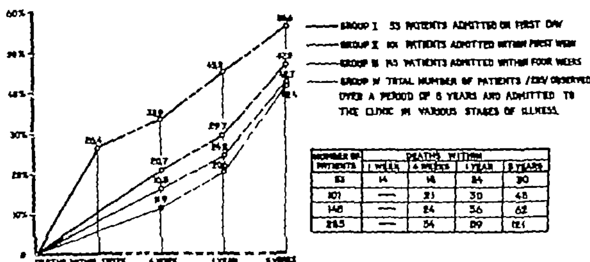
The first workers to investigate the subject of mortality in patients who survived myocardial infarction were Bland and White in 1941.[3]

We sent a questionnaire to 432 patients discharged from the clinic in order to gain information on their fate. The information received on 412 patients (95.3 per cent) showed that 124 had died outside the clinic.

To obtain a more exact evaluation of the time when patients died during the 5 years subsequent to the first attack, we selected 285 patients who had been under our observation for at least 5 years or longer and who had been treated from 1948 to the end of 1954. So that there

Table II

Occupation group	*Number of people in each group*	*Number of cases of myocardial infarction*	0/00	*Significance test (t)*	
Mental workers	56 346	136	2.41	Mental workers—craftsmen	3.1
Craftsmen	31 023	49	1.58	Mental workers—physical workers	13.9
Physical workers	149 816	27	0.18	Craftsmen—physical workers	6.1
Total	237 185	212	0.89		



NUMBER OF PATIENTS	DEATHS WITHIN			
	1 WEEK	4 WEEKS	1 YEAR	5 YEARS
53	14	18	24	30
101	—	23	30	48
148	—	24	56	62
285	—	54	89	121

Fig 2 Percentage of mortality in patients with cardiac infarction (cumulative curve) The numbers in each group are cumulative. The first group consisted of 53 patients. The second group consisted of the 53 patients of the first group plus 48 others, for a total of 101 The third group consisted of the 101 patients of the second group plus 44 others, for a total of 145 The fourth group consisted of the 145 patients of the third group plus 140 others for a total of 285

would be still more uniformity of the material in regard to the time of admittance of the patients to the clinic we divided these 285 patients into 4 groups the first group consisted of 53 patients admitted to the clinic within 24 hours of the onset of illness, the second of 101 patients admitted up to the end of the first week after the onset of illness and the third of 145 patients admitted to the clinic up to the end of the fourth week after the first attack. An analysis of these groups is shown in Fig 2

The first group of 53 patients provides the best opportunity for estimating the time of survival after myocardial infarction and is more convenient to use for purposes of comparison It follows from the graph for this group that the largest number of patients died during the first week after the first attack of myocardial infarction (14 or 26.4 per cent) The numbers then slowly rise reaching 18 (33 9 per cent) after the first 4 weeks 24 (45 2 per cent) after a year and 30 (56.6 per cent) after 5 years of observation. Lukomskij[11] White[22] and Friedberg[4] also emphasize that the greatest mortality in patients with myocardial infarction is during the first few days of illness.

The percentages for the second group of patients, who were admitted to the clinic up to a week after the onset of illness closely approximate those of White[22] who found in his material that 19 per cent died after 4 weeks and those of Richards, Bland and White[19] who found that 51 per cent died after 5 years.

The data from the other two groups of patients shown in Fig 2 are figures which serve rather for general orientation as to the fate of patients after myocardial infarction since there was no possibility of any strict follow up of the time such as is evident in the first group.

A comparison of the curves in Fig 2 will show one of the reasons for the divergence of the figures given by other authors in estimating the mortality of patients after myocardial infarction. A larger number of patients included from the first hours or days after the onset of illness gives a greater mortality in the particular center of investigation

When discussed from the social point of view the problem assumes still greater significance if we take into consideration the circumstance that as a result of cardiac infarction according to the data of Friedberg[4] Chwilickaja[3] and Lukomskij[11] varying degrees of circulatory insufficiency appear in almost 50 per cent of the patients who live often considerably limiting their capacity for work.

For comparison with others, we also have made an analysis of the survival rate of patients discharged from the clinic after myocardial infarction.

Out of 225 patients discharged from the clinic, 18 (8 per cent) died within a year and 66 (29.3 per cent) died within 5 years. Björk and associates[1] with material collected in the same manner found a slightly greater percentage of mortality among the patients discharged from their clinic, i.e. 11 per cent of deaths after 1 year and 34 per cent after 5 years.

Summary and Conclusions

A study of the case histories and a follow-up of the fate of 520 patients treated for myocardial infarction in 1948-1960 at the Medical Clinic in Cracow has resulted in the findings listed below

1 The annual number of patients with myocardial infarction admitted to the clinic had risen in the tenth year of observation to three times the initial number

2 In general men suffer myocardial infarctions almost five times as frequently as do women (1:4 9) In our observations, cardiac infarction appeared in women only after the age of 40 and the number of women suffering from this then rose reaching a ratio in relation to men of 1:2 6 after the age of 70

3 The highest morbidity of myocardial infarction in both sexes occurred most frequently between the ages of 50 and 60 years, with 40 7 per cent of the patients concentrated in this age group 91 per cent of all sufferers from myocardial infarction were found to be between the ages of 40 and 70

4 We have found hypertension in 56 per cent of the female and 30 per cent of the male patients with myocardial infarction—hence, almost three times as frequently as it is found in general among the same population

5 The first week is the most dangerous for patients who survive the first attack of myocardial infarction since 26 per cent of the patients die within this period. The mortality increases to 34 per cent by the end of the fourth week to 45 per cent during the first year and to 56.4 per cent by the end of the fifth year Of the patients discharged from the clinic 8 per cent died within a year and 29 3 per cent within 5 years.

6. The concurrence of diabetes gives a markedly worse prognosis in regard to the length of life after myocardial infarction.

7 In 83 patients who died in the clinic within the first 6 weeks after acute myocardial infarction postmortem examinations confirmed the clinical diagnosis of myocardial infarction in 90.3 per cent of the cases, and with the exception of one case general atherosclerosis was found in all subjects.

REFERENCES

1 Björk, G Sievers J Blomqvist, G Studies on myocardial infarction in Malmö, 1935-1954 Acta med scandinav 163:(2) 81 1958.
2. Bland, E. F and White, P D Coronary thrombosis, J.A.M.A. 117 1171 1941
3 Chudzikiewicz, T Occupation, age and seasons of the year and the myocardial infarction, Pol. Tyg Lek. 12:(24) 901 1957
4 Chudzikiewicz, T The aetiopathogenesis of myocardial infarction, Pol. Tyg Lek 16:(28) 1066, 1961
5. Chwilichaja, M L Prognosis in cardiac infarction, Terap Arkh. 27:(2) 3 1955
6. Dock, W Why are men's coronary arteries so sclerotic? J.A.M.A. 170:(2) 132, 1959
7 Dybkaer R., Poulsen, H and Friedberg, R. Macroscopic heart changes in 141 consecutive cases of myomalacia cordis, Danish M Bull 7:(1) 9 1960.
8 Friedberg C K Diseases of the heart Philadelphia, 1956, W B Saunders Company p 920.
9 Friedberg, R Dybkaer R., and Poulsen, H. The epidemiology of coronary occlusion in Denmark, Danish M. Bull. 7:(1) 1 1960
10 Goldstein, F Jensen, W K., Waldron, J M and Duncan, G. G. The relationship between hypertension and coronary occlusion, Ann. Int. Med. 41:(3) 446 1956.
11 Hornela, T The treatment of myocardial infarction with anticoagulants, Kardiol Polska 1 1/2) 195, 1954.
12. Lober P H. Pathogenesis of coronary sclerosis, A.M.A. Arch Path. 55:(5) 357 1953
13. Lukomskij P E., and Parow E M The background and cause of myocardial infarction Soveta. Med. 21:(1) 3, 1957
14. Martin, W J Distribution in England and Wales of mortality from coronary disease, Brit. M. J 1 1523 1956.
15 Morgan, A. D The pathogenesis of coronary occlusion, Oxford, 1956, Blackwell.
16. Richards, D W Bland, E. F and White P D Cited by Björk, et al.
17 Rinzler S. H. The clinical aspect of arteriosclerosis, Springfield, Ill 1957 Charles C Thomas.

18. Statistical Yearbook 1959 Issued by the Chief Office of Statistics, Warsaw 1959
19. Tochowicz L., Krol, W., Stylo, D and Pudlik, Z. Norms of arterial pressure and frequency of hypertension among the population of the district of Cracow Pol. Arch. Med. Wewnet. 26:(4) 483 1954
20. Tochowicz, L Pasyk, S., and Demkiewicz, W Studies on blood cholesterol and alimentary lipemia in atheromatosis. Clinical evaluation, Pol. Tyg Lek. 15:(20) 737 1960
21. White, P D Heart disease, New York, 1956 The Macmillan Company p. 555
22. Wolkowa, K. G. The morphogenesis of coronary atherosclerosis and its significance in secondary changes in the myocardium, Klinica Medic. 34:(5) 1 1956.

Arterial pressure and hypertensive disease in a West Indian Negro population

Report of a survey in St. Kitts, West Indies

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Negroes in the United States seem to have a greater tendency to hypertensive disease than do whites.[1,2] This characteristic has been interpreted by some as evidence of racial factors, presumably genetic, and by others as a consequence of environmental stress, notably psychologic. These alternatives cannot be evaluated readily in the complex environment of the United States. The present report describes a study of a Negro population whose remote origin is similar to that of the North American Negro but whose socioeconomic environment, culture, and ancestry are more uniform than those of most United States Negroes.

Such groups occur in the Lesser Antilles, of which St. Kitts in the Leeward Islands is one. During a visit there in 1957, Dr. R. L. Turnbull of the Cleveland Clinic gained the impression from physicians that hypertensive disease was common and that the high degree of organization of the Government Health Service would facilitate a survey of this or other problems. A plan was developed for a cooperative field study by the staff members of the University College of the West Indies and the Cleveland Clinic Foundation. Subsequently, arrangements for coding and tabulation were made in consultation with one of us (F. E. M.). Major aims were first, to determine distributions of arterial pressure in adults, and second, to evaluate relative severity of hypertensive disease in subjects with diastolic hypertension. These data form the substance of this report. Concurrent observations on aspects of nutrition and ischemic heart disease are reported elsewhere.[3]

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Locale

St Kitts (St Christopher) was named by Columbus, colonized by the British and French in 1623 and became part of the (British) Leeward Islands Colony in 1713 James Grainger M D hailed it in his poem The Sugar Cane (London 1766) lines 60 to 67

'Such green St. Christopher thy happy soil
Not Grecian Tempe where Arcadian Pan
Knit with the Graces, tun d his sylvan Pipe
Not purple Enna
Can vie, blest isle, with thee

At that time it was a flourishing economic and cultural center its rich sugar plantations were worked by African slaves until slavery was abolished in *1833* Descendants of former slaves now form some 98 per cent of the population

Land area is 68 square miles. The birth rate in 1957 was 52 and the crude death rate 15 per 1,000 40 per cent of the population was less than 15 years of age population density was about 800 per arable square mile. Living standards and income were well below North American levels wages of laborers in 1954 were about $7 00 (U.S) weekly during full employment and have not increased greatly since Total population is about 35,000 * of whom some four fifths live in villages and work on neighboring plantations, whereas most non Negroes who are sedentary clerical and factory workers, live in Basseterre the capital The villages are linked at intervals of a few miles by a perimetric coastal road

Medical and health services of the villagers are provided almost entirely by the Government Health Service which is administered by the Senior Medical Officer The several Health Districts of the island are based on village Health Centers each is administered by a District Medical Officer and staffed by a Sanitary Inspector a Public Health Nurse a midwife and a pharmacist

Some 74 per cent of live births are classed as illegitimate[4] This arises from the custom of keeper unions in these a woman termed a home domestic and her children are provided for but do not enter into a paternal family group

*Data based on official estimates.

Procedures

Study group The field work was carried out in early 1958 Since essential hypertension manifests itself in early or middle adult life the study was done on subjects who were 20 to 49 years of age * Dr Harney** suggested that representative samples of the total rural and village population of some 28 000 of all ages could be found in three villages, namely Sandy Point (2 700) Old Road (700) and Cayon (1 000) † The former two villages are on the southwest, and the latter one is on the northwest coast. Although they are not far apart social communication between villages seems limited

With the cooperation of the Government Health Service and in order to induce adults of desired ages to come to the Health Center for examination at appropriate times the village Sanitary Inspector and a member of the survey staff visited dwellings in turn until a responsible adult in each had been interviewed and given appointment cards for relevant occupants.

In the age group of 20 to 49 years, 566 of 686 men (83 per cent) and 881 of 992 women (89 per cent) who had been given cards came for examination The local Public Health Nurse was unable to relate nonresponse to current health status, of which she was usually well aware. Failure to respond affected households and seemed attributable to suspicion or to fear of venipuncture even when these people were reassured new appointments made and venipuncture omitted unless requested those who had not responded at first still avoided examination

Far from not responding 241 subjects came to the clinics without appointment cards either young men in small groups or persons in the company of friends for whom appointments had been made. Their motives seemed to be casual interest impatience or congeniality Half of the men in this subgroup were 20 to 29 years

*† Cayon, and, as the survey ended, in other villages, cards were left for occupants who were [illegible] to [illegible] years old. Response of this group was poor and those who came to clinics were often uncertain of their exact age. Accordingly data from these are omitted from, or only incidentally listed in, the tabulations of this report
**Lennox Harney M D D P H District Medical Officer
†Numbers in parentheses are rough estimates of inhabitants

old. Together these walk ins constituted 18 per cent of the men and 12 per cent of the women examined.

Table I indicates distribution of the island s estimated population by age and sex and of the total group examined and its subgroups. Correspondences in proportions between the estimates and examined group suggest that the sample was representative.

Table II compares the means of systolic pressures between subgroups, viz. respondents and walk ins, people of different villages and those of apparent Negro and mixed race. Since there are no indications of systematic differences in this characteristic, data from subgroups were combined in the tabulations that follow

The method of selection of population—purposive selection of villages with an attempt to secure 100 per cent coverage of the age group 20 to 49—does not permit the estimation of sampling errors. However the closeness of agreement of the results for the three villages, as shown in Table II increases our confidence that the subjects examined are reasonably representative of the rural population of the island with respect to the variables studied

Documentary corroboration of age was *not obtained. Detailed distributions of* terminal digits of stated ages showed a uniform spread of digits from 0 through 9 among men among women, 15.3 per cent reported ages in even multiples of 10 and 8 7 to 10 6 per cent in digits 1 through 9 Furthermore, most of the 1 447 respondents seemed certain of their ages within a year or two they often revised relatives estimates listed on appointment cards.

Table I Estimated population of St. Kitts 1951 and population included in the survey of blood pressure made in three villages 1958 by sex and age

Sex and age	*Population of St. Kitts, 1951**	*Three-village survey 1958*			
		Cards issued	*Card-holders examined*	*Walk-ins*	*Total examined*
Number of persons					
Males, total	10 980	686	566	123	689
20–29	4 080	246	210	67	277
30–39	3 400	196	163	25	188
40–49	2 270	189	163	25	188
50–59	1 230	37	30	6	36
Age unknown	—	18	—	—	—
Females, total	12 090	992	881	118	999
20–29	4 000	344	308	35	343
30–39	3 300	287	262	32	294
40–49	2 840	264	250	35	285
50–59	1 950	83	61	16	77
Age unknown	—	14	—	—	—
Per cent distribution, persons 20 to 49 yr					
Males, 20–49 yr	100	100	100	100	100
20–29	42	39	39	57	42
30–39	35	41	30	21	29
40–49	23	30	30	21	29
Females, 20–49 yr	100	100	100	100	100
20–29	39	38	35	31	37
30–39	33	32	32	28	32
40–49	28	30	30	31	[illegible]

*Official estimates; last census 1946.

Table II Mean levels of systolic blood pressure by sample status race village and sex and age

	Males			Females		
	20–29	*30–39*	*40–49*	*20–29*	*30–39*	*40–49*
Mean systolic blood pressure (mm. Hg)						
By sample status						
Card-holders	135 8	140 4	142 8	126 0	139 0	155 8
Walk-ins	135 0	132 0	148 3	130 4	135 5	148 5
By race						
Negro	136 2	139 2	144 0	126 5	138 8	155 3
Mixed	129 7	140 4	139 4	126 0	136 6	150 5
By village						
Sandy Point	136 4	140 9	140 4	127 1	137 1	154 3
Old Road	139 2	139 7	148 6	124 9	139 7	156 5
Cayon	133 6	136 4	143 7	126 5	140 1	154 5
Number of persons examined						
Total	277	188	188	343	294	285
By sample status						
Card holders	210	163	163	308	262	250
Walk ins	67	25	25	35	32	35
By race						
Negro	254	172	167	313	268	258
Mixed	23	16	21	30	26	27
By village						
Sandy Point	123	92	85	145	143	128
Old Road	40	38	50	54	66	66
Cayon	114	58	53	144	85	91

Table III Zero as terminal digit of recorded blood pressure

Study	Total number recorded	Systolic		Diastolic	
		Number ending in zero	*Per cent ending in zero*	*Number ending in zero*	*Per cent ending in zero*
Comstock (1957)	1 162	363	31 2	424	36 5
Master et al.[a] (1952)	15 711	7 210	45 9	8 036	51 1
St. Kitts	1 688	1 041	61 7	898	53 2

Examination Blood pressure" clinics were established in village Health Centers. Each center consisted of a waiting room two offices and a pharmacy. During the survey clinics the offices were used as examining rooms and the pharmacy as a laboratory. A nurse who was familiar with idiom and customs received subjects in the waiting room and verified information on the card noting name sex age (to last birthday) and her estimates of descent (Negro or mixed) and of physical activity in work (sedentary medium or heavy). Pregnancies and the complications thereof were also recorded. Height (sole to vertex shoes removed) and weight were

measured garments were light and standard Samples of urine were obtained from 1 650 subjects who represented 96 per cent of the women and 98 per cent of the men the urine was tested with Uristix for protein and glucose. Abnormal proteinuria was frequently confirmed by sulfasalicylic turbidimetry with good agreement of estimates between methods. The subject was then ushered to a cot in an examining room.

Here a physician inquired as to past or present illness. If this enquiry elicited a recital of symptoms suggestive of cardiovascular or renal disease, more detailed information was sought. Arterial pressure was measured after a rest of 5 to 10 minutes. Then at the beginning of the survey venous blood was sampled in most subjects late in the survey venipuncture was done only in subjects who seemed to be ill or who had diastolic hypertension. The technique for the measurement of pressure followed the recommendations made by the American Heart Association in its Special Report of 1951[8] diastolic pressure was noted as the point of cessation of sound or if sounds persisted to very low levels as the point of muffling Observations were made an hour or more after the subjects had eaten and exercised during rest in recumbency indifferently

*Table IV Levels of blood pressure (mm Hg) by sex and age**

Sex and age	*Number of persons*	*Systolic*		*Diastolic*		
		Mean	*Standard deviation*	*Mean*	*Standard deviation*	*100 mm. or more (%)*
Males						
20–29	277	135 6	16 14	79 2	10 12	4 3
20–24	151	134 7	15 96	78 0	9 62	2 0
25–29	126	136 8	16 29	80 7	10 49	7 1
30–39	188	139 3	18 17	83 0	11 98	12 2
30–34	105	138 2	17 34	82 0	11 69	9 5
35–39	83	140 7	19 08	84 2	12 22	15 7
40–49	188	143 5	22 75	86 0	13 78	16 0
40–44	93	138 5	18 90	84 1	11 62	14 0
45–49	95	148 4	25 82	87 8	15 40	17 9
50–59	36	152 3	25 78	89 2	14 37	22 2
50–54	29	150 3	24 58	88 0	12 49	20 7
55–59	7	(160 6)	(32 68)	(94 3)	(21 78)	(28 6)
Females						
20–29	343	126 5	15 85	76 4	11 66	5 0
20–24	191	125 5	14 67	74 6	10 26	2 1
25–29	152	127 8	17 13	78 6	12 88	8 6
30–39	294	138 6	22 67	84 7	13 96	15 6
30–34	168	134 7	18 68	82 8	13 75	12 5
35–39	126	143 7	26 23	87 2	13 82	19 8
40–49	285	154 9	30 44	90 6	15 33	27 7
40–44	142	151 0	28 49	88 8	15 33	22 5
45–49	143	158 7	31 79	92 3	15 13	32 9
50–59	77	168 5	34 82	93 8	16 00	40.3
50–54	60	167 5	33 85	93 6	15 76	40 0
55–59	17	172 2	38 98	94 6	17 28	41 2

*In this and subsequent tables, statistics based on fewer than 30 cases are shown in parentheses.

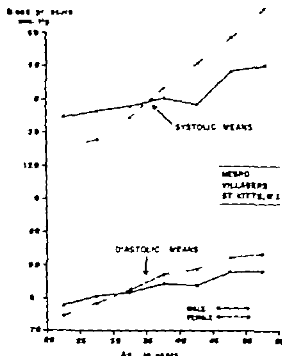


Fig 1 Means of systolic and diastolic blood pressures

from the right or left arm a 12-cm. hook-on cuff and a standardized aneroid manometer were used. Although pressures were to be recorded in multiples of 2 or 5 the data (Table III) show a distinct preference for zero as the terminal digit.

The basic datum of this report is the examiner's average of the first two or three determinations of pressure made in sequence over 1 or 2 minutes. Subjects (190 men and 265 women) who seemed anxious and/or whose blood pressure or pulse rate seemed high at this observation were reassured and kept at rest for second determinations 10 to 15 minutes later determinations were repeated in a few after an additional hour of rest in the waiting room and at a second visit a day or two later. These determinations of pressure and pulse usually gave lower values than did first readings. These data are omitted from this report.

Observations

1 Means of blood pressures Data are presented as means (Fig 1) and means and standard deviations (Table IV) of systolic and diastolic blood pressures. Means and to a somewhat greater degree variability of the distributions increased with age. Mean systolic pressures in women exceeded those in men at about ages 35 to 39 and diastolic pressures at ages 30 to 34 years thereafter both pressures rose more steeply in women than in men. Table V enables comparison of the means of the data obtained at St. Kitts with the home-recorded blood pressures of urban Negroes and whites of Nassau, Bahamas,[6] and the clinic records of rural Negroes and whites of Muscogee County Georgia,[7] and of a large, substantially white, urban group in Framingham Massachusetts.[8] The systolic pressures of the three Negro groups are alike and are higher than those of white groups. The means of systolic pressure of Negro men and of white women begin to rise steeply at about age 45. The means of diastolic pressures of Negro women but not of Negro men are higher than those of white groups.

2 Frequency distribution of blood pressure. Basic tables of frequency distribution of blood pressures for each sex by 5-year age groups were prepared. These data are summarized in Appendix Tables I through VI (see pp. 624-627) as histograms (Fig 2) and as cumulative frequency curves (Fig 3,*A* C) Proportions of individuals with high arterial pressures (over 160 mm. Hg systolic or 100 mm. Hg diastolic) increased with age accordingly curves projected along the histograms flatten and skew toward high pressures with increasing age. The cumulative curves facilitate estimates of proportionate distributions they show that the blood pressures of women were distributed in lower ranges than were those of men at ages 20 to 29 were nearly the same at ages 30 to 39 and exceeded those of men at ages 40 to 49

3 Prevalence of hypertension The arbitrary character of segregation used in classifying high arterial pressures as hypertension is implied in the use of quotation marks and of multiple criteria. Those of Table VI include the criteria suggested by a committee of the World Health Organization (WHO) on recommendation of the Brookline Conference[9] together

*It is proposed to deposit these (A.D.I. Tables I to IV, inclusive) with the American Documentation Institute

with others in common use.* The prevalence of hypertension by any of the criteria listed increases with age. When groups of like age are compared, systolic hypertension is more common in men but diastolic hypertension is equally distributed between the sexes at ages 20 to 39. Prevalences by the various criteria are similar at ages 30 to 39 and those of systolic and/or diastolic hypertension as compared at ages 40 to 49 are about twice as great in women as in men.

*These are estimates prepared from Appendix Tables I-VI.

Reference to Table 9 of the Framingham data [9] even when allowance is made for the use of two rather than one estimate of blood pressure with resultant regression toward the mean indicates a much lower prevalence of definite hypertension than in Kittitians, especially among women.

4. *Ponderal (height-weight) index and blood pressure.* Of the several expressions of body weight in relation to stature, that selected was Sheldon's ponderal index[10]; this is height to the nearest inch divided by the cube root of weight to the nearest pound. The values ranged from less than

Table V. Comparison of findings in surveys of blood pressure in Negro populations in St. Kitts, Bahamas, and Georgia and in white populations in Bahamas, Georgia, and Massachusetts

Sex and age	*Negro*			*White*		
	St. Kitts	*Bahamas**	*Georgia*	*Bahamas**	*Georgia*	*Mass.*
Mean systolic blood pressure (mm. Hg)						
Male						
25–34	137.5	134.4	132.9	127.7	121.5	
35–44	139.6	142.5	142.8	130.0	123.8	134.1
45–54	149.3	150.2	150.6	133.0	132.6	139.9
Female						
25–34	131.1	129.5	124.9	120.2	112.6	
35–44	147.2	144.7	146.8	132.3	120.9	128.4
45–54	162.8	154.3	158.2	145.0	135.5	147.0
Mean diastolic blood pressure (mm. Hg)						
Male						
25–34	81.3	85.2	81.1	75.6	78.5	
35–44	84.2	91.5	91.5	82.0	82.5	85.8
45–54	87.9	93.8	96.2	83.2	86.1	88.4
Female						
25–34	80.6	82.4	80.1	72.7	72.3	
35–44	88.0	89.4	90.5	81.9	76.9	81.6
45–54	92.9	91.9	93.6	86.0	82.5	89.4
Number of persons studied						
Male						
25–34	231	156	21	68	40	
35–44	174	122	34	44	65	748
45–54	124	104	25	34	59	632
Female						
25–34	320	214	44	72	87	
35–44	268	196	47	52	96	928
45–54	203	121	32	35	62	744

*Comparable data not available.

Note: Data for St. Kitts, Bahamas, and Massachusetts were originally reported for 5-year age groupings. Means reported in this table are weighted means of the 5-year age group components, with weights proportional to the total U. S. population in these age groups in 1940. Means for Georgia are unweighted means as originally reported.

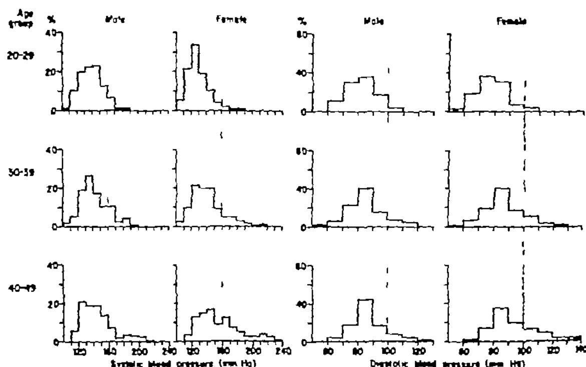


Fig. 2. Frequency distributions of systolic and diastolic blood pressure by age and sex.

12 (overweight) to 13.5 or more (underweight). These interpretations may not apply precisely to heavily muscled Kittitians; however, indices of about four fifths of the subjects lay between the extremes. Men showed some tendency to gain weight with age but were infrequently (1 in 20) overweight; proportions of underweight men (about 1 in 10) were nearly constant among age classes. Among women, the proportion who were overweight increased from 13 per cent at ages 20 to 29 to 31 per cent at 30 to 39 and 35 per cent at 40 to 49, with concurrent decreases in the proportion who were underweight.

Five ranges of ponderal index are listed with age and sex groupings of means of systolic and diastolic pressures in Table VII. Differences in pressures between categories were small and irregular, but systolic pressures in women and, to a lesser degree, diastolic pressures in both sexes tended to increase with weight and age. The sharp increases observed in overweight women who were 40 to 49 years of age were not corrected for artifacts of arm size;[11] these may have contributed to the apparent increments in pressure.

Hypertension and hypertensive disease

A second aspect of the survey was characterization of the status of subjects with diastolic hypertension (100 mm. Hg or more) so as to gain some insight into the nature of the hypertensive state and the severity of concomitant hypertensive vascular disease. Techniques were limited by conditions of the field survey in a medically unsophisticated population. The 245 subjects presenting diastolic hypertension were closely questioned as to family history, work status, and symptoms referable to cerebral, cardiac, or renal dysfunction, and the women were questioned with regard to parity and toxemia of pregnancy. Signs of cerebrovascular disease were sought by brief neurologic tests and funduscopy, signs of cardiac disease by symptoms and electrocardiographic evidence of left ventricular hypertrophy, and signs of renal disease by estimates of proteinuria and, in many subjects, of creatininemia.

1. Work status. Diastolic hypertension could not be associated with work status, perhaps because so few (less than 4 per cent of the subjects) engaged in light or sedentary work, and because of indefinite

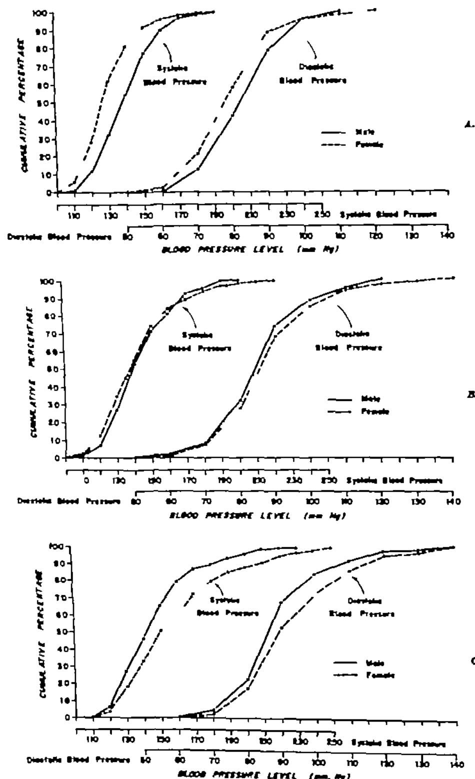


Fig. 3. Cumulative frequency distributions of levels of systolic and diastolic blood pressure. *A*, Males and females, aged 20-29. *B*, Males and females, aged 30-39. *C*, Males and females, aged 40-49.

Table VI Prevalence of hypertension by sex and age in St. Kitts villagers

Sex and age	WHO criteria* Normotension	Borderline	Hypertension	160/100† mm. Hg	Systolic 160 or more	Diastolic 100 or more
	Per cent of persons					
Males						
20–29	50 5	35 4	14 1	12 6	9 7	4 3
30–39	49 5	26 1	24 5	22 9	18 6	12 2
40–49	44 1	28 2	27 7	24 5	20 7	16 0
Females						
20–29	79 0	14 0	7 0	5 0	4 4	3 0
30–39	51 7	24 1	24 1	20 7	16 3	15 6
40–49	31 6	23 9	44 6	42 5	40 7	27 7

*Criteria for population studies prepared by WHO Expert Committee on Cardiovascular Disease and Hypertension (WHO/CVD & II/14 27 October 1958) *Normotension*, Systolic B.P below 140 and diastolic B.P below 90 mm. Hg *Hypertension* Systolic B P 160 or more and/or diastolic B P 95 or more. *Borderline*: All other

†Systolic B P 160 or more and/or diastolic B P 100 or more

distinction between moderate and heavy work

2 *Family history* The character of many family unions and lack of under standing of the nature of illness made this inquiry fruitless

3 *Pregnancy parity and toxemia* Pregnancy was listed as such in the first or at least in the second and third trimesters Association of current pregnancy and parity with blood pressure are summarized in Table VIII Diastolic pressures in the pregnant women were lower than those in the nonpregnant woman at ages 25 to 39 and systolic pressures were lower at ages 30 to 39 means of pressures were not affected by pregnancy at ages 20 to 29

Hypertension was no more common in those women (the majority) who had four or more pregnancies than in those who had had only one to three (Table IX) However subjects who had experienced toxemia of pregnancy (characterized by edema proteinuria and hypertension which were discovered when the women were attending prenatal clinics) showed a greatly increased prevalence of hyper tension when compared with women whose pregnancies had progressed normally Nulliparity seemed to be associated with in creased prevalence of hypertension at ages 30 to 39

4 *Symptoms* The symptoms were not usually informative. Possibly as an expression of presbyopia most older people had dim eyes. Few complaints were elicited from men women readily complained of headache backache and pain in the belly bottom Nocturia seemed to be a domestic ritual among both sexes and at all ages.

5 *Cerebrovascular disease* Only two of the entire sample who were examined showed signs of previous strokes Both were among the 245 persons with diastolic hypertension

Funduscopic examinations were made on 176 hypertensive subjects after pupillary dilation with cyclopentolate hydro chloride. Factors evaluated were arteriolar constriction and sclerosis[13] and hemorrhages exudates and papilledema[13] results of the examinations were summarized by Keith Wagener Barker grades[14]

Fundal abnormalities (Table X) were found in 85 per cent of the hypertensive subjects prevalence and grades of retinopathy increased with rising diastolic pressures fundi were abnormal in all with diastolic pressures of 120 mm Hg or more Papilledema was found in one subject diastolic pressure in this person was only 104 mm. Hg and proteinuria was greater than 100 mg per 100 ml

6 *Cardiac symptoms.* Symptoms were graded[13] in 112 hypertensive subjects. Of these, 98 were classed in functional Grades 0 or 1 12 were in Class 2 and 1 each was in Classes 3 and 4. Rheumatic heart disease constrictive pericarditis, and aneurysmal dilatation of the aorta were each diagnosed once.

Electrocardiograms (subject supine 3 standard and 3 unipolar limb leads and 6 precordial leads) were recorded in 243 of 271 men who were 35 to 49 years old and in 131 of 143 women who were 45 to 49 years old. These records included 42 of 43 men and 45 of 47 women with diastolic hypertension. Criteria used in the diagnosis of left ventricular hypertrophy were modifications[16] of those of Sokolow and Lyon [17] Results are listed in Table XI Of 2 men who had left ventricular hypertrophy one had diastolic and the other systolic hypertension with aortic insufficiency Diastolic hypertension was present in all 8 women who had left ventricular hypertrophy Other abnormalities, such as nonspecific myocardial changes, remote myocardial infarction, and right bundle branch block, were almost as common (about 1 in 8) in the electrocardiograms of those men without as in those with diastolic hypertension (1 in 5)

7 *Renal symptoms.* Proteinuria was estimated in 643 of 653 men and 909 of 922 women who were 20 to 49 years of age

Table VII *Mean levels of blood pressure by ponderal index (height/ $\sqrt[3]{\text{weight}}$) sex and age*

Sex and age	*Ponderal index*				
	Less than 12 0 (Heavy ←	*12 0–12 4*	*12 5–12 9*	*13 0–13 4*	→ *13 5 and over Light)*
Mean systolic blood pressure (mm. Hg)					
Males					
20–29	(150 3)	139 4	135 7	133 7	131 3
30–39	(133 0)	143 1	137 8	138 6	139 8
40–49	145 1	144 2	141 7	144 6	126 1
Females					
20–29	128 9	126 6	126 1	126 0	125 6
30–39	146 0	140 9	134 7	136 6	139 4
40–49	164 7	150 0	156 7	145 9	136 7
Mean diastolic blood pressure (mm. Hg)					
Males					
20–29	82 9	82 9	79 1	78 7	74 9
30–39	80 0	85 0	83 2	81 9	81 4
40–49	90 0	86 5	86 9	83 9	78 0
Females					
20–29	79 6	76 1	77 2	75 7	72 9
30–39	88 4	85 7	84 0	84 7	81 7
40–49	93 8	89 3	91 6	86 2	83 6
Number of persons					
Males					
20–29	7	38	130	78	23
30–39	8	36	64	62	16
40–49	16	33	81	40	14
Females					
20–29	41	63	106	70	24
30–39	81	67	58	45	12
40–49	97	84	46	44	10

*Excludes pregnant women.

Table VIII. Mean levels of blood pressure in women by age and current pregnancy status

Pregnancy status	Age 20–24	25–29	30–34	35–39
Mean systolic blood pressure (mm. Hg)				
Not pregnant	125.7	127.6	136.4	145.3
Pregnant	123.7	128.7	121.0	126.9
Mean diastolic blood pressure (mm. Hg)				
Not pregnant	74.8	79.1	83.9	88.2
Pregnant	73.2	74.8	73.3	77.0
Number of persons				
Not pregnant	172	135	150	115
Pregnant	19	17	18	11

Table IX. Per cent of women with diastolic blood pressure of 100 mm. Hg or more by age toxemia and history of pregnancy

Parity and toxemia status	Age 20–29	30–39	40–49
Per cent of women with diastolic blood pressure of 100 mm. Hg or more			
Never pregnant	3.5	25.6	32.4
No history of toxemia			
1 to 3 pregnancies	5.8	8.6	23.6
4 or more pregnancies	4.9	13.4	23.2
History of toxemia	19.0	36.7	61.5
Number of women			
Never pregnant	65	39	37
No history of toxemia			
1 to 3 pregnancies	137	81	72
4 or more pregnancies	81	112	142
History of toxemia	21	30	26

*Excludes women who were pregnant at the time of survey

Among those in whom the diastolic pressures were less than 100 mm. Hg the prevalence of abnormal proteinuria (20 mg per 100 ml. or more) ranged from 5 to 7 per cent and was 12 per cent in men who were 40 to 49 years old (Table XII). Among those with diastolic hypertension the prevalence was not increased at ages 20 to 29 but increased with age thereafter. Associations of proteinuria with hypertension are shown in Table XIII. The prevalence increased with systolic pressure in excess of 140 mm. Hg at ages 20 to 39 years and with pressures of 160 or more at ages 40 to 49 years it increased regularly with diastolic pressures over 80 mm. Hg in both age groups.

Concentrations of serum creatinine were measured in 272 subjects, of whom 73 had diastolic hypertension (Table XIV). In normotensive men and women creatininemia corresponded with normal levels in North American subjects[14] the average increased in hypertensive individuals.

8. Relative severity of hypertensive disease. The unreliability of symptoms, limited facilities lack of repeated measurements of blood pressure over long periods and loss of a number of samples of serum and urine limited this analysis to 87 subjects with diastolic hypertension and rendered inapplicable a severity index used in the trials of therapeutic drugs.[15] The estimate used was based on selected criteria viz. retinopathy of Grade 2 or more left ventricular hypertrophy by electrocardiogram and abnormal proteinuria of 20 mg per 100 ml or more any of which was classed as a stigma of hypertensive disease. Among 35 men and 52 women 39 showed no stigma of hypertensive disease 41 showed one and 22 showed two or more (Table XV). The most common stigma was retinopathy and the next most frequent was proteinuria.

Table X. Distribution of persons with levels of diastolic blood pressure of 100 mm. Hg or more by level of blood pressure and grade of retinopathy

	Diastolic blood pressure (mm. Hg) 100–109	110–119	120 or more
Per cent of persons			
All grades	100	100	100
Grade 0	25	10	0
Grade 1	57	49	33
Grade 2	14	27	33
Grade 3 or 4	4	14	33
Number of persons	77	63	36

*Includes only persons whose optic fundi were examined.

9 Association with sodium chloride

A. SERUM ELECTROLYTES. Means of concentrations (Table XVI) in agreement with the observations of others[illegible] were alike as between normotensive and hypertensive individuals and correspond to North American normal values.[11]

B. CONSUMPTION AND EXCRETION Intake of brackish water was considered to be a possible explanation for the high prevalence of hypertension among Bahamian Negroes, although subsequent studies[illegible] have suggested that other factors are of more importance In contrast the water on St. Kitts is collected in mountain catchments, and our analyses showed a content of Na of less than 15 mg per liter However meat and fish are commonly preserved by salting The possible associations of the intake of salt were studied in two ways.

First, frozen homogenates of samples which represented three daily adult servings were collected from four families in each of the three villages and analyzed.* Moisture averaged 76.6 per cent Na and Cl per volume of moisture yielded averages per day of 1 85 Gm of Na (range of 1 0 to 2.6) and 6.27 Gm. of Cl (range 5 4 to 8.0) These levels correspond to average United States estimates (see Table 31 in Reference 18) Since the local custom is not to salt food after cooking nor to take salt between meals the analyses probably represent average daily intake.†

Second casual specimens of urine were analyzed for Na Cl and creatinine. The considerations in mind were that the creatinine content would represent daily output in a range of ±30 per cent,[illegible] and that daily output in this group of 128 men and 208 women would average about 1 Gm so that the milliequivalents of Na or Cl per milligram of creatinine would represent a little less than the electrolyte output for 1 minute. Data summarized in Table XVII show that the Na and Cl contents were alike in corresponding age sex, and blood-pressure groups at ages 20 to 39 years. The output of electrolytes in hypertensive subjects seemed greater than in normotensive subjects at ages 40 to 49 but wide individual variability detracts from the possible significance of this difference. In the group as a whole the mean output corresponds to about 10 Gm of NaCl daily This estimate corresponds well with that from analysis of food. Furthermore the data on urine do not indicate any regular association between the output of salt and by inference, the intake of salt and the occurrence of hypertension.

*By the Army Medical Nutrition Laboratory Fitzsimons Army Hospital, Denver Colo., through the courtesy of Lt. Col. L. M. Hursch, MC, USA, and M C. F Consolazio.

†For completeness, it is noted that the Ca content of the mixture by weight averaged 1.13 Gm. daily

Comment

1 Procedures The bases for assuming that the sample is representative of the island's rural population and justification for combining data from subgroups were noted above. The nurses estimate that only 10 per cent of the subjects were of mixed race indicates racial homogeneity Stated ages were apparently not seriously in error however when possible documentary verification of this datum is desirable. The distribution of terminal digits of arterial pressures yields greater zero perference in our data (as in those of Master Garfield and Walters[illegible]) than that in Comstock's data[7] agreement of our means with those he obtained from Negro laborers in Georgia suggests that zero preference has not significantly distorted our data. Most of his measurements and all of Johnson and Remington's[8] were made in the subjects homes, whereas ours were made in the privacy of a Health Center with which the subjects were familiar agreement of means in the three groups may indicate that locale makes little difference.

2 Means distributions and prevalence Means of blood pressures in the various Negro groups are higher than those in white populations. Estimates of prevalence indicate that hypertension is more common among Negroes, especially women than among whites of like ages. With advancing age progressive skewing of the histograms and flattening of the curves of cumulative distribution of pressure occur This can be considered to represent the appearance in age classes of increasing proportions of persons with "hypertension"[illegible] or age-conditioned increments of pressure in most of the population.[illegible] Like other

Table XI Electrocardiographic finding of left ventricular hypertrophy (LVH) by sex age and diastolic blood pressure

Sex age and diastolic blood pressure (mm. Hg)	Number of ECGs recorded	Electrocardiographic findings			Number of ECGs not recorded
		Normal	LVH	Other abnormalities	
Males					
35–39	70	65	—	5	13
Diastolic, less than 100	57	53	—	4	13
Diastolic, 100 or more	13	12	—	1	—
40–44	87	74	—	13	6
Diastolic, less than 100	74	64	—	10	6
Diastolic 100 or more	13	10	—	3	—
45–49	86	68	2	16	9
Diastolic, less than 100	70	57	1	12	8
Diastolic, 100 or more	16	11	1	4	1
Total 35–49	243	207	2	34	28
Diastolic, less than 100	201	174	1	26	27
Diastolic, 100 or more	42	33	1	8	1
Females					
45–49	131	107	8	16	12
Diastolic, less than 100	86	78	—	8	10
Diastolic, 100 or more	45	29	8	8	2

cross-sectional surveys, our data do not resolve the current epidemiologic controversy as to the nature of essential hypertension Rather as McKusick[17] has suggested a solution may come from a longitudinal study in a population as homogeneous as possible in racial background and environmental circumstances, conditions which are fulfilled by the population of St. Kitts.

Parenthetically the fact that the means of pressure and prevalence of hypertension among white women exceed those of men at ages 45 to 50 years has contributed to the belief in a menopausal hypertension. The fallacy of this association is shown by the fact that means of pressure of Negro women begin to exceed those of men at ages 35 to 39 and also that castration does not provoke hypertension in young women.[13]

3 Ponderal index and blood pressure Obesity is much less common in Kittitian laboring men than in the urban white groups. Definite obesity with massive arms seemed to us to be less common in Kittitians than in middle-aged Negro women in the United States, where by another estimate these *average* more than 20 per cent overweight.[19] Furthermore a gain in weight by mature Kittitian women is due in part to increased muscle mass. Possibly because Kittitians tend to be muscular rather than obese associations between blood pressure and body weight are less striking in our subjects than in other surveys.

4 Hypertension and hypertensive disease

A. PREGNANCY TOXEMIA, AND NULLIPARITY Current pregnancy did not depress means of pressures in women who were 20 to 24 years old in whom diastolic hypertension is uncommon whereas pregnancy decreased means in older women many of whom were presumably hypertensive. This association accords with the view that pregnancy is an antihypertensive state in man[19] as it is in experimentally hypertensive animals.

Pyelonephritis is a cause of hypertension

Table XII. Per cent of persons with proteinuria of 20 mg. per 100 ml. or more by sex, age, and level of diastolic blood pressure

Sex and diastolic blood pressure (mm. Hg)	Age		
	20-29	30-39	40-49
Per cent of persons with proteinuria (20 mg./100 ml. or more)			
Males			
Diastolic, less than 100	5 0	5 5	12 1
Diastolic, 100 or more	8 3	14 3	26 7
Females			
Diastolic, less than 100	5 0	7 0	5 4
Diastolic, 100 or more	5 9	13 2	23 1
Number of persons			
Males			
Diastolic, less than 100	260	165	157
Diastolic, 100 or more	12	21	30
Females			
Diastolic, less than 100	322	244	202
Diastolic, 100 or more	17	46	78

Includes only persons for whom the level of urine protein was measured

and has been studied epidemiologically from this aspect in Jamaica and in Wales,[21] where the blood pressures of those with bacteriuria increased with parity. The fact that in St. Kitts the means of pressures were not higher in women who had had four or more pregnancies than in those who had had one to three suggests that pyelonephritis does not account for most of the hypertension observed in these women.

The association of hypertension with nulliparity at ages 30 to 49 years is unexplained except as a like association has been described in childless men and women in two European surveys.[22,23]

Finally, the strong association between previous toxemia of pregnancy and subsequent diastolic hypertension substantiates the view now widely held that toxemia is a cause of persistent hypertension.[24,25]

B. SIGNS AND SEVERITY OF HYPERTENSIVE DISEASE.

Cerebral. Signs of cerebrovascular disease were infrequently severe; only 2 of 245 subjects with diastolic hypertension demonstrated stroke residuals, and the proportion who showed severe fundal changes (Grade III or more) was also small (13 5 per cent). If Grade IV retinopathy is accepted as an index of the syndrome of malignant hypertension, this condition seems to be relatively uncommon in Kittitians. In other hypertensive groups it is usually estimated as occurring in 1 or 2 per cent.

Cardiac. The fact that signs of left ventricular hypertrophy were observed in only 9 of the 87 subjects also accords with the view that hypertensive disease is relatively mild; earlier onset of hypertension in women than in men probably accounts for the fact that this finding was made in 8 women and only 1 man.

Table XIII. Per cent of persons with proteinuria of 20 mg. per 100 ml. or more by age and level of blood pressure

Level of blood pressure (mm. Hg)	Age	
	20-39	40-49
Per cent of persons		
Systolic		
Less than 130	4 5	11 0
130-139	3.4	7 6
140-159	10 4	5 9
160-179	9 5	10 8
180 or more	10 3	29 9
Diastolic		
Less than 80	4 2	9 0
80-89	5 9	8 1
90-99	8 8	9 2
100-109	11 3	13 2
110 or more	14 7	34 5
Number of persons		
Systolic		
Less than 130	441	100
130-139	235	79
140-159	286	135
160-179	84	74
180 or more	39	77
Diastolic		
Less than 80	452	89
80-89	389	173
90-99	148	87
100-109	62	88
110 or more	34	88

*Table XIV Mean level of serum creatinine by sex and levels of diastolic blood pressure**

Diastolic blood pressure (mm. Hg)	Sex	
	Male	Female
Mean serum creatinine (mg %)		
Diastolic less than 100	1 00	0 85
Diastolic 100 or more	1 45	1 12
Number of persons†		
Diastolic less than 100	81	118
Diastolic 100 or more	17	56

*Data for persons aged 20-49 combined
†Includes only persons for whom serum creatinine was measured

Table XV Occurrence of stigmata of hypertensive disease in villagers with diastolic hypertension (100 mm Hg or more)

Sex and age	Stigmata of hypertension		
	None	One	Two or more
Per cent of persons			
Males			
35-44	63	31	5
45-59	43	19	37
Females			
45-59	38	37	25
Number of persons			
Males			
35-44	12	6	1
45-59	7	3	6
Females			
45-59	20	19	13

Renal Prevalence of proteinuria increased at ages 40 to 49 years in subjects with normotension and among those with hypertension at ages 30 to 39 but not at ages 20 to 29 Among hypertensive subjects this is attributable to the slow development of nephrosclerosis which also accounts for increased serum creatinine in some with hypertension. However the highest serum creatinine observed was 4.5 and there were only 4 among 73 individuals with diastolic hypertension whose concentrations were greater than 3 0 mg per 100 ml The regular association between diastolic pressure greater than 90 mm Hg and proteinuria suggests that 20 mg per 100 ml is indeed an upper level of normal proteinuria by the method used The age distribution of subjects with excess proteinuria indicates that renal disease is sequential to persistent hypertension rather than causal and the association with diastolic pressure that proteinuria may be an index of nephrosclerosis in field surveys of hypertension

Relative severity of hypertensive disease A unique aspect of this survey was the attempt to study the clinical significance of hypertension as well as its numerical distribution This objective was not achieved to the extent desired although we have shown that such evaluation is feasible in a field survey The data obtained in this respect would be more valuable if there were comparable data on the prevalence of hypertensive disease in a random sample of a population with diastolic hypertension As it is the distribution of abnormalities gave us the impression that the hypertensive disease observed in St. Kitts is not severe. However this estimate is based on our experience in clinics and

*Table XVI Mean levels of serum sodium and chloride by sex and levels of diastolic blood pressure**

Diastolic blood pressure (mm. Hg)	Sex	
	Male	Female
Mean serum sodium (mEq./L.)		
Diastolic less than 100	140 9	139 5
Diastolic, 100 or more	139 8	138 4
Mean serum chloride (mEq./L.)		
Diastolic, less than 100	101 4	102 2
Diastolic 100 or more	103 0	102 7
Number of persons†		
Diastolic less than 100	121	173
Diastolic, 100 or more	19	57

*Data for persons aged 20-49 combined
†Includes only persons for whom serum sodium and chloride were measured

Table XVII Mean ratios of urine chloride/creatinine and sodium/creatinine by sex age and levels of diastolic blood pressure

Sex and diastolic blood pressure (mm. Hg)	Age	
	20-39	40-49
Mean chloride/creatinine ratio		
Males		
Diastolic, less than 100	207	171
Diastolic, 100 or more	173	209
Females		
Diastolic, less than 100	189	158
Diastolic, 100 or more	182	185
Mean sodium/creatinine ratio		
Males		
Diastolic, less than 100	204	167
Diastolic, 100 or more	179	215
Females		
Diastolic, less than 100	183	156
Diastolic, 100 or more	181	186
Number of persons		
Males		
Diastolic, less than 100	60	37
Diastolic, 100 or more	15	16
Females		
Diastolic, less than 100	99	33
Diastolic, 100 or more	35	41

*Includes only persons for whom urine chloride, sodium, and creatinine were measured.

hospitals where patients with symptomatic hypertensive disease tend to congregate.

5 *Nature of the hypertension* Although examinations were limited it seems unlikely that with the probable exception of hypertension subsequent to toxemia of pregnancy most of the hypertension observed was primarily renal. Rather like primary or essential hypertension in other groups diastolic hypertension in Kittitians increased in prevalence with age was more common in women than in men was followed rather than preceded by proteinuria and up to age 50 was infrequently severe. Similarities of means of blood pressure of Kittitians to those of other North American Negroes suggest a greater concentration in these groups than in white individuals of the genetic factor or factors which make for essential hypertension. We would anticipate therefore, that this trait would also be as prevalent in West Africans, the forebears of these people however recent studies in Nigeria[33] and Liberia[34] suggest that this is not the case. Unpublished observations by one of us (R.E.S.) demonstrate that means of blood pressure of an urban Jamaican group are lower than those of a rural group Since the genetic factor is equal these observations imply existence of significant environmental factors (e.g. nutrition infection etc.) that may diminish increased arterial pressures of groups otherwise possibly predisposed to hypertension.

Negatively in the United States the social environment and diet particularly intake of salt do not seem to be determinants of the high prevalence of hypertension in North American Negroes. Speculatively the greater resistance of American Negroes than of whites to anticholinergic drugs[37,38] suggests the possibility that a difference in autonomic, particularly vasomotor tone may be a contributory cause and should be evaluated

Summary and conclusions

The means of systolic and diastolic arterial pressures of 1,575 Negro villagers of St. Kitts West Indies, aged 20 to 29 years, are higher than those of white groups of like age in the Bahamas and in the United States after about age 30 years means of blood pressures are higher in Kittitian women than in men at 35 years of age and over

This population tends to be muscular rather than commonly obese means of pressures show only moderate associations with increasing body weight (decreasing ponderal index) except among women aged 40 to 49 in whom the recorded pressures may have been increased by the artifact of arm size. The intake of sodium chloride at meals and the output in the urine are not excessive output shows no definite association with distribution of arterial pressures.

The survey was unique in that it aimed at assessment of severity as well as prevalence of hypertension. Data indicate that the hypertension is not often severe in the age group studied; the syndrome of

malignant hypertension was encountered doubtfully only once in 275 subjects with diastolic pressures of 100 mm. Hg or more. Fundal changes greater than Grade II were uncommon as were electrocardiographic signs of left ventricular hypertrophy and creatininemia of renal failure. The common manifestations of hypertensive vascular disease were mild retinal changes (Grades I or II) and slight proteinuria Although this assessment was less complete than we hoped that it would be the practicality of clinical evaluation in field surveys has been established

Since the means of blood pressures of Kittitians parallel those of Bahamian and Georgian (United States) Negroes the predisposition of American Negroes to arterial hypertension seems to be a racial trait which might be advantageously studied in terms of levels of autonomic function.

We deeply appreciate the assistance of Dr and Mrs. Ralph Lambert, Dr Kenneth Standard, Patricia Maynard, R.N and Pearl Walters, R.N., as members of the field group, and the help given by Colonel H A. C. Howard Administrator and Dr J M Semple, Chief Medical Officer and his staff which includes District Medical Officers, Chief and District Sanitary Inspectors, and District Public Health Nurses, as well as that of many others.

Appendix Tables I VI Frequency distribution of blood pressures for each sex by age groups

Appendix Table I *Distribution of levels of blood pressure systolic by diastolic males aged 20 to 29 years*

Systolic blood pressure	*Total*	*Diastolic blood pressure*													
		Less than 65	*65-69*	*70-74*	*75-79*	*80-84*	*85-89*	*90-94*	*95-99*	*100-104*	*105-109*	*110-119*	*120-129*	*130-139*	*140 and over*
Total	277	16	18	49	34	68	32	43	5	8	3	1			
Less than 110	4	3		1											
110-119	29	4	6	13	4	2									
120-129	55	3	5	12	11	17	4	3							
130-139	63	1	4	12	8	19	11	8							
140-149	64	5		6	8	19	8	14	3	1					
150-159	35		3	3	2	5	6	8	1	4	2	1			
160-169	18			2	1	4	2	7	1		1				
170-179	4					1	1	1		1					
180-189	3					1		2							
190-199	1									1					
200-209	1									1					
210-219															
220-229															
230-239															
240-249															

Appendix Table II *Distribution of levels of blood pressure systolic by diastolic: males aged 30 to 39 years*

Systolic blood pressure	*Total*	*Diastolic blood pressure*													
		Less than 65	*65-69*	*70-74*	*75-79*	*80-84*	*85-89*	*90-94*	*95-99*	*100-104*	*105-109*	*110-119*	*120-129*	*130-139*	*140 and over*
Total	188	8	8	18	26	46	31	23	5	11	2	9	1		
Less than 110	4	2	1	1											
110-119	10	2	2	2	3	1									
120-129	36	3	2	5	11	11	4								
130-139	50		3	7	8	19	6	6	1						
140-149	33			2	1	9	12	6	1	2					
150-159	20	1		1	1	1	6	3	1	5		1			
160-169	20				2	3	3	5	1	2	1	2	1		
170-179	5							2	1		1	1			
180-189	8					1				2		5			
190-199	1							1							
200-209	1					1									
210-219															
220-229															
230-239															
240-249															

Appendix Table III *Distribution of levels of blood pressure systolic by diastolic: males aged 40 to 49 years*

Systolic blood pressure	*Total*	*Diastolic blood pressure*													
		Less than 65	*65-69*	*70-74*	*75-79*	*80-84*	*85-89*	*90-94*	*95-99*	*100-104*	*105-109*	*110-119*	*120-129*	*130-139*	*140 and over*
Total	188	4	4	19	15	54	30	24	8	12	3	9	3	2	1
Less than 110															
110-119	11	1	2	4	3	1									
120-129	40	1	1	10	5	16	6	1							
130-139	36	1		4	5	14	9	3							
140-149	36			1	1	13	11	6	3	1					
150-159	26		1		1	7	3	5	3	6					
160-169	14					2	1	6		3	1	1			
170-179	4								1	2		1			
180-189	7							1			1	3		1	1
190-199	6					1		2	1			2			
200-209	5	1									1	1	2		
210-219	1											1			
220-229	2												1	1	
230-239															
240-249															

Appendix Table IV. Distribution of levels of blood pressure, systolic by diastolic, females aged 20 to 29 years

Systolic blood pressure	Total	Diastolic blood pressure: Less than 65	65-69	70-74	75-79	80-84	85-89	90-94	95-99	100-104	105-109	110-119	120-129	130-139	140 and over
Total	343	31	42	79	46	75	30	18	5	8	2	4	1	2	
Less than 110	20	12	7	1											
110-119	75	9	21	31	10	3	1								
120-129	117	5	11	34	17	39	9	1				1			
130-139	67	3	3	9	14	21	11	6							
140-149	35	2		4	4	9	5	9	1	1					
150-159	14				1	2	4	1	2	4					
160-169	7					1			2	2	1	1			
170-179	3							1		1			1		
180-189	3										1	2			
190-199															
200-209	1													1	
210-219															
220-229	1													1	
230-239															
240-249															

Appendix Table V. Distribution of levels of blood pressure, systolic by diastolic, females aged 30 to 39 years

Systolic blood pressure	Total	Diastolic blood pressure: Less than 65	65-69	70-74	75-79	80-84	85-89	90-94	95-99	100-104	105-109	110-119	120-129	130-139	140 and over
Total	294	14	10	34	24	74	43	38	11	22	7	8	3	6	
Less than 110	8	4		3	1										
110-119	29	5	3	14	4	3									
120-129	64	1	3	12	13	31	2	2							
130-139	59	4	4	3	3	26	13	5		1					
140-149	59			2	3	9	21	15	5	4					
150-159	27					3	5	6	5	6		2			
160-169	14					2	1	5		4	1	1			
170-179	15						1	4	1	3	3	2	1		
180-189	8							1		1	2	2	2		
190-199	5									2	1			2	
200-209	1											1			
210-219	2									1				1	
220-229	1													1	
230-239															
240-249														2	

Appendix Table VI. Distribution of levels of blood pressure: systolic by diastolic, females aged 40 to 49 years

Systolic blood pressure	Total	Diastolic blood pressure: Less than 65	65–69	70–74	75–79	80–84	85–89	90–94	95–99	100–104	105–109	110–119	120–129	130–139	140 and over
Total	285	3	3	18	24	63	38	38	19	27	11	25	5	9	2
Less than 110	1	1													
110–119	11		1	5	3	2									
120–129	38	1	1	6	14	13	3								
130–139	44		1	5	2	23	9	4							
140–149	50			2	4	18	15	8	2	1					
150–159	25	1				1	8	7	4	3	1				
160–169	36				1	4	3	9	8	9	1	1			
170–179	22							4	4	5	3	6			
180–189	15					2		5		4	1	3			
190–199	8							1		2	2	2		1	
200–209	8								1	1	1	4	1		
210–219	11									1	1	4	2	3	
220–229	8									1	1	4	1	1	
230–239	3											1		1	1
240 and over	5												1	3	1

REFERENCES

1. Bays, R. P. and Scrimshaw, N. S. Facts and fallacies regarding the blood pressures of different regional and racial groups, *Circulation* 8:655, 1953.
2. Phillips, J. H., Jr., and Burch, G. E. A review of cardiovascular disease in the white and Negro races, Medicine 39:241, 1959.
3. Stuart, K. L., Schneckloth, R. A., Lewis, L. A., Moore, F. E., and Corcoran, A. C. Diet, serum cholesterol, protein, blood haemoglobin, and glycosuria in West Indian Negroes, with observations on ischemic heart disease, Brit. M. J. (submitted for publication).
4. Health Department, St. Christopher-Nevis and Anguilla: Annual Report for the Year 1957, Basseterre, 1958.
5. Bordley, J., III, Connor, C. A., Hamilton, W. F., Kerr, W. J., and Wiggers, C. J. Recommendations for human blood pressure determinations by sphygmomanometers, Circulation 4:503, 1951.
6. Johnson, B. C., and Remington, R. D.: A sampling study of blood pressure levels in white and Negro residents of Nassau, Bahamas, J. Chron. Dis. 13:39, 1961.
7. Comstock, G. W. An epidemiologic study of blood pressure levels in a biracial community in the southern United States, Am. J. Hyg. 65:271, 1957.
8. Kagan, A., Gordon, T., Kannel, W. B., and Dawber, T. R. Blood pressure and its relation to coronary heart disease in the Framingham study. Skelton, F. R., editor: Hypertension, Vol. VII, New York, 1958, American Heart Association.
9. Conference on Longitudinal Cardiovascular Studies, held at Brookline, Mass., June 17 and 18, 1957.
10. Sheldon, W. E., Dupertuis, C. W., McDermott, E. Atlas of man: a guide for somatotyping the adult male of all ages, New York, 1954, Harper & Brothers.
11. Pickering, G. W., Roberts, J. A. F., and Sowry, G. S. C. The etiology of essential hypertension. 3. The effect of correcting for arm circumference on the growth rate of arterial pressure with age, Clin. Sc. 13:267, 1954.
12. Wagener, H. P., Clay, G. E., and Gipner, J. F. Classification of retinal lesions in presence of vascular hypertension: report submitted by committee, T. Am. Ophth. Soc. 45:57, 1947.
13. Lockhart, G., vonNoorden, G., Dustan, H. P., Corcoran, A. C., and Page, I. H. The course of retinopathy in treated malignant hypertension, A.M.A. Arch. Int. Med. 106:205, 1960.
14. Keith, N. W., Wagener, H. P., and Barker, N. W. Some different types of essential hypertension, their course and prognosis, Am. J. M. Sc. 197:332, 1939.

Table I The depth of Q_{V6} in normal children

Reference	Patients	Age group	Number of cases	Per cent Q_{V6} by size (mm.)				
				< 1	1	2	3	4+
Braudo[2]	Normal newborn infants	0-24 hr	24	83	17	0	0	0
		24-72 hr	25	96	4	0	0	0
Walker[4]	Premature infants	0-24 hr	30	87	10	3	0	0
		24-72 hr	24	83	17	0	0	0
		3-7 days	16	81	6	6	0	6
		8-30 days	19	63	32	0	0	5
Ziegler[8]	Normal children	See Reference 2						

experience the presence of a Q_{V6} of increased depth is the most specific feature of left ventricular diastolic overloading and the most useful to follow in serial electrocardiograms.

Other types of abnormal left precordial Q waves occur. The Q wave of myocardial infarction has been thoroughly studied but is rare in children. It was noted in our series of anomalous left coronary artery arising from the pulmonary artery.[9]

Case material

Groups of cases which represented the major cardiological problems in the field of pediatrics were studied and 994 cases were included in the tabulation. With severe malformations, only postmortem material was included, whereas with less severe lesions surgical, catheterized, and other clinical cases were accepted as indicated in Table II. Cases of dextroposition were eliminated, but otherwise all available suitable cases studied in each category were included. The electrocardiograms were all recorded by means of Sanborn direct writing equipment at the Hospital for Sick Children. We did not make allowance for the age of the patient but this factor appears to be unimportant after the first week of life. Although the tables do not show the serial changes in individual patients when several electrocardiograms were available, we chose for tabulation the most recent one prior to operative correction. We noted only the depth of the wave, not the width, because in childhood the Q_{V6} is almost always narrow. We regard a Q_{V6} of less than 1 mm. to be well within the normal range, a Q_{V6} of 1 to 2 mm. as of minor significance, and a Q_{V6} of 2 mm. or more as of more significance.

Atrial septal defects. Analysis of patients with atrial septal defects generally showed few with a deep Q_{V6}. We believe that the relatively small Q_{V6} in cases of ostium secundum type of atrial septal defect is due to the fact that the shunt at the atrial level does not overload the left ventricle. However, in those patients with atrioventricularis communis, 33 per cent had a Q_{V6} of 3 mm. or more. A tendency to congestive failure with elevated pressure in the atria and also insufficiency of the mitral valve are frequently present in the ostium primum syndrome. Either or both of these factors may contribute to left ventricular diastolic overloading and thus to the genesis of a deep Q_{V6}.

Ventricular septal defects. A group of patients with ventricular septal defects was previously studied by Vince and Keith.[8] This group had the largest percentage with deep Q waves in Lead V_6. In 80 per cent the Q_{V6} was over 1 mm., and in 43 per cent it was 3 mm. or more. The average Q_{V6} was deeper in the patients with the largest pulmonary to systemic flow ratios. In those in whom surgical correction was made, the Q_{V6} usually diminished in size postoperatively.

Patients with evidence by catheterization of pulmonary hypertension (right ventricular systolic pressure of 90 mm. Hg or more) and a pulmonary to systemic

flow ratio of less than 2 had an average Q_{V6} of 0.6 mm. There were 8 such cases 6 patients with pure right ventricular load ing and an average Q_{V6} of 0.2 mm. and 2 with combined ventricular loading and an average Q_{V6} of 2 mm. These patients who had combined ventricular loading and pulmonary to systemic flow ratios of 2 or

Table II The depth of Q_{V6} in heart disease of infancy and childhood

Condition	*Source*	*Total number of cases*	*Per cent Qv by size (mm.)*				
			<1	*1*	*2*	*3*	*4+*
Ostium secundum	Operation	65	68	14	14	2	3
Ostium primum	Postmortem	15	67	0	20	7	7
Atrioventricularis communis	Postmortem	15	40	20	7	20	13
Ventricular septal defect							
Nonsurgical	Catheterization	104	21	20	16	16	26
Preoperative	Operation	27	7	30	22	7	33
Postoperative			26	19	15	22	19
Patent ductus arteriosus							
Preoperative	Operation	167	23	17	22	16	22
Postoperative			39	33	14	10	4
Combinations of defects							
VSD and PDA	Postmortem or operation	19	53	21	11	5	11
Ostium secundum and VSD	Postmortem	11	36	18	18	18	9
Ostium secundum and partial anomalous pulmonary venous return	Postmortem or operation	8	87	0	13	0	0
Coarctation of the aorta							
<1 yr with VSD or PDA	Operation or postmortem	41	70	10	15	0	5
>1 yr with VSD or PDA		9	22	0	22	11	44
<1 yr without VSD or PDA		12	83	0	17	0	0
>1 yr without VSD or PDA		35	71	14	9	3	3
Aortic stenosis							
Postmortem cases	Postmortem	14	71	21	0	0	7
Surgical cases, living	Operation	7	85	0	0	0	14
Uncomplicated cases	Clinical	57	54	32	11	2	2
Cases with aortic insufficiency	Clinical	10	40	10	30	10	10
Cases with other complications	Clinical	7	57	43	0	0	0
Pulmonary stenosis with normal aortic root	Catheterization and/or operation	93	59	22	16	2	1
Corrected transposition	Postmortem or angiography	16	81	13	0	0	6
Total anomalous pulmonary venous return	Postmortem	27	96	4	0	0	0
Transposition of the great vessels	Postmortem	70	73	13	6	6	3
Tetralogy of Fallot							
Typical cases with no operation	Postmortem and clinical with angiography	45	89	11	0	0	0
Typical cases before shunt		14	71	29	0	0	0
Same cases after shunt			57	14	14	14	0
With pulmonary atresia	Postmortem	17	94	6	0	0	0
Atypical tetralogy of Fallot	Clinical	14	43	7	36	14	0
Pulmonary atresia with normal aortic root	Postmortem	16	81	13	6	0	0
Tricuspid atresia							
Without transposition	Postmortem	17	47*	35	18	0	0
With transposition		3	100*	0	0	0	0
Mitral atresia with normal aortic root	Postmortem	11	100	0	0	0	0
Aortic atresia	Postmortem	28	93	0	4	0	4

*[illegible] patient with transposition had any Q wave, but all those without transposition had at least [illegible] small Q wave.
VSD: Ventricular septal defect. PDA: Patent ductus arteriosus.

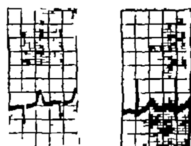


Fig. 1. Patent ductus arteriosus in Patient D. W. Lead V_6. *Left*, Preoperatively at age 4 years. *Right*, Two years after ligation of the ductus, at age 6 years.

more presented with deeper Q waves in Lead V_6. Thus the degree of pulmonary vascular resistance and the degree of left ventricular loading was reflected in the electrocardiogram.

Patent ductus arteriosus (see Fig. 1). There was a large percentage of the patients with patent ductus arteriosus who had a deep Q_{V6}, and this group had the largest percentage with very deep Q waves. Ligation of the patent ductus arteriosus produced a nearly uniform significant reduction in the depth of Q_{V6}. Of the patients who had patent ductus arteriosus, 30 per cent had a Q_{V6} of 5 mm. or more. After ligation of the ductus the average Q_{V6} changed from 2.6 mm. to 1.3 mm. In some cases a reduction of several millimeters occurred, often within a few weeks after the operation.

Combination of defects. Combinations of defects produced interesting clinical problems. Those patients who had a ventricular septal defect combined with another lesion producing a left-to-right shunt had a definitely smaller average Q_{V6} than that found in either those with simple ventricular septal defect or those with simple patent ductus arteriosus. We had expected that the combination of ventricular septal defect and patent ductus arteriosus would produce a greater proportion of deep Q waves in Lead V_6 than we found. On further consideration, however, we realized that a large proportion of these patients were infants who had a much greater degree of pulmonary hypertension than did those with the isolated lesions. The Q_{V6} was not remarkable in a group with ostium secundum type of atrial septal defect plus ventricular septal defect. The combination of ostium secundum and partial anomalous pulmonary venous return causes no left ventricular diastolic overload, and in only one such case was the Q_{V6} of more than 1 mm.

Coarctation of the aorta. Left ventricular systolic overloading, as in aortic stenosis and coarctation of the aorta, is said to be characterized by a left precordial pattern of initial Q wave followed by tall, broad R waves, with an intrinsicoid deflection greater than 0.04 second associated with flattened or inverted T waves.[4]

In patients under the age of 1 year there were few cases of coarctation of the aorta with a sizable Q_{V6}, regardless of the presence or absence of associated patent ductus arteriosus or ventricular septal defect, but in patients over 1 year of age those who had these associated defects which cause diastolic loading tended to have deep Q waves in V_6, whereas those with uncomplicated cases did not. Clinically, those patients with coarctation of the aorta in whom the diagnosis was made before they were 1 year old presented differently from those in whom the diagnosis was made at a later date, since most of the patients under 1 year of age had an associated patent ductus and more frequently the coarctation was preductal. There was also a higher incidence of associated severe malformations in those in whom the diagnosis was made before they were 1 year old. Presumably the hemodynamics were different from those in the older age group, and we thought that pulmonary hypertension, which was often present, and the early age militated against a significant Q_{V6} in these cases.

Aortic stenosis. Similarly, few patients with congenital aortic stenosis had a deep Q_{V6}, *except* those who had associated aortic

Table III. *Criteria of left ventricular diastolic overloading in patent ductus arteriosus*

	Average size (mm.)		
	Q_{V6}	R_{V6}	T_V
Preoperative	2.6	20.8	2.7
Postoperative	1.3	13.9	2.3

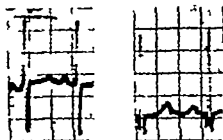


Fig. 2. Before and after a Blalock operation. Lead V_6. *Left*: Preoperatively June 1, 1956. *Right*: Postoperatively Dec. 12, 1959.

insufficiency and who therefore, also had left ventricular diastolic overloading.

Aortic insufficiency. Among our cases of aortic insufficiency of rheumatic origin we rarely found a Q_{V6} of significantly increased depth presumably because the insufficiency was of recent origin and mild in degree.

Cyanotic congenital heart disease. In cyanotic congenital heart disease the Q wave in Lead V_6 exhibited only a few interesting features. A deep Q_{V6} is uncommon in transposition of the great vessels (15 per cent of the patients had a Q_{V6} of 2 mm. or more) but may occur in this and some other congenital cyanotic conditions.

In tetralogy of Fallot, a Q_{V6} of 2 mm. or more was seen in only 7 per cent of the patients and was confined to the following groups with diastolic loading of the left ventricle: (a) atypical cases" with predominant left-to-right shunt, (b) cases after a Blalock-Taussig shunt operation, (c) unusual cases such as that of pulmonary insufficiency and large left-to-right shunt, and that of a left superior vena cava entering the left atrium (see Fig. 2).

In typical cases of tetralogy of Fallot prior to operation a Q_{V6} of 1 to 2 mm. was seen in only 15 per cent, and in none was the Q_{V6} deeper than 2 mm.

Pileggi and associates[19] found a Q wave in Leads V_5 and V_6 in 24 per cent of 142 cases of tetralogy of Fallot, and they also noted that this tended to be associated with mild cyanosis and left ventricular enlargement, as it was in our experience.

Only 6 per cent of the patients who had pulmonary atresia with normal aortic root and 15 per cent of those who had tricuspid atresia, had a Q_{V6} of 2 mm. or more. We expected deeper Q waves in Lead V_6 in patients with these malformations because they have left ventricular diastolic overloading. However, a Q wave in Lead V_6 is not common in early infancy at the time that most of these cases are seen and we believe that the presence of any Q_{V6} at this age is significant.

Patients with tricuspid atresia without transposition of the great vessels all had a detectable Q_{V6}, whereas none of those with transposition had any Q_{V6}. This interesting observation is not an absolute rule, however, since cases which do not fit this finding have been reported.[11,23]

Endocardial fibroelastosis. Several patients with primary endocardial fibroelastosis of the usual dilated type exhibited deep Q waves in Lead V_6. Forty per cent had a Q_{V6} of 2 mm. or more. The only patient with the contracted form of endocardial fibroelastosis had no Q in Lead V_6.

Origin of the left coronary artery from the pulmonary artery. This condition produces left ventricular myocardial damage early and the deep Q_{V6} sometimes seen in this condition is due to myocardial death. Our cases have been reported previously.[4]

Idiopathic cardiomegaly. The large Q_{V6} (6 mm.) in our patient with idiopathic cardiomegaly developed in the earlier years of his illness and then diminished in depth. At postmortem examination the ventricular septum was 40 mm. thick and the left ventricular free wall was 20 mm. thick. The ventricular septum appeared to have hypertrophied first producing a strong left-to-right force and thus, a deep left precordial Q wave, which was later offset by a strong right-to-left force produced by the left ventricular free wall as it too hypertrophied.

Congenital complete heart block. We wondered whether the increased stroke volume necessitated by congenital complete heart block might be equivalent to ventricular diastolic overloading but the Q waves in Lead V_6 in this condition were mostly of normal size.

Corrected transposition of the great vessels. The Q wave was absent or insignificant in 81 per cent of the patients with corrected transposition of the great vessels. In this

Table IV Criteria of left ventricular diastolic overloading in ventricular septal defect

Number of cases	Pulmonary to systemic flow ratio	Right ventricular pressure (mm.Hg)	Average size (mm.)		
			Q_{V6}	R_{V6}	T_{V6}
8	1–2	>90	0.6	10	3.4
37	1–2	<90	2.9	16	3.3
23	2–3	Only 4 patients in these groups had a right ventricular pressure over 90 mm Hg hence, these groups were not subdivided	2.0	15	1.9
17	3–4		2.7	17	2.7
27	4 or more		3.7	21	3.0

condition the ventricles are transposed. If there were also transposition of the ventricular conduction system this would explain the usual absence of a Q_{V6} in this condition as noted in our cases and by other observers,[13] and it would also explain why a Q wave is usually seen in Lead V_1.

Discussion

A review of the electrocardiographic findings in our case material confirms the concept that a deep Q wave in the left precordial leads is one of the features of left ventricular diastolic overloading; furthermore it is the most frequent single indication of left ventricular diastolic overloading and a change in the depth of Q_{V6} is a most useful indication of a change in left ventricular diastolic overloading. Tall peaked T waves have been referred to as indicative of such an overload. We have found the Q in Lead V_6 to be more characteristic. Furthermore tall peaked T waves were frequently not noted even in the presence of clear evidence of left ventricular diastolic overload.

We compared three electrocardiographic features (depth of Q, height of R, and height of T, all in Lead V_6) as indicators of left ventricular diastolic overload in patent ductus arteriosus and ventricular septal defect. In patent ductus arteriosus the postoperative change in hemodynamics was best reflected by Q_{V6} rather than by R_{V6} or T_{V6} (see Table III). However, in the subgroups of ventricular septal defect the correlation of flow ratios with the R wave in Lead V_6 was more consistent than with the Q wave in Lead V_6, even if full allowance were made for those cases of right ventricular hypertension and relatively little left-to-right shunt. Both correlated better than did the T wave in Lead V_6. The amplitude of R_{V6} increases in both left ventricular systolic overloading and diastolic overloading, whereas Q_{V6} is either normal or diminished in left ventricular systolic overloading. Thus, a deep Q_{V6} is more specific for diastolic overloading (see Table IV).

Other conditions which produce a deep Q_{V6} include hypertrophy of the left ventricular portion of the septum and myocardial injury. The ventricular complexes of myocardial injury differ from those of left ventricular diastolic overloading in that they feature a small or absent R wave, a delayed intrinsicoid deflection, and often characteristic S-T-segment and T wave changes.

Summary

The electrocardiograms of nearly one thousand patients with congenital heart disease were studied with particular reference to the Q wave in Lead V_6. (1) Patients with left ventricular diastolic overloading, especially when it was associated with a left-to-right shunt, developed a deep Q_{V6}. (2) If the degree of diastolic overloading changed, the depth of Q_{V6} changed correspondingly (e.g., ligation of a patent ductus reduced the size of Q_{V6}). (3) The depth of Q_{V6} was the most useful single indicator of left ventricular diastolic overloading. (4) Patients who had ventricular

septal defect with much left ventricular diastolic loading characteristically had a significant Q_{V6}. Those with increased pulmonary vascular resistance had smaller or no Q_{V6}. (5) A significant Q wave in Lead V_6 (2 mm or more) in patients with tetralogy of Fallot was almost invariably associated with a larger than usual pulmonary blood flow and therefore less cyanosis and the Q wave again indicated a good left ventricular diastolic load (6) Origin of the left coronary artery from the pulmonary artery may produce myocardial infarction with an associated deep Q_{V6} but this should not be confused with the electrocardiographic findings in left ventricular diastolic overloading

REFERENCES

1. Sodi-Pallares, D and Calder R. M New bases of electrocardiography St. Louis, 1956, The C. V Mosby Company p. 382.
2. Ziegler R. F Electrocardiographic studies in normal infants and children, Springfield, Ill., 1951 Charles C Thomas, Publisher
3. Brando M., Unpublished data.
4. Ueber R. Unpublished data.
5. Cabrera, C. E., and Monroy J R. Systolic and diastolic loading of the heart, Am. Heart J 43:661 1952
6. Agustsson, M. G DuShane J W and Swan, H. J C. Ventricular septal defect in infancy and childhood, Pediatrics 20:848, 1957
7. DuShane, J W Weidman, W H. and Brandenburg R. O The electrocardiogram in children with ventricular septal defect and severe pulmonary hypertension correlation with response of pulmonary arterial pressure to surgical repair Presented at the meeting of the American Pediatric Society Buckhill Falls, Pa., May 1959
8. Keith, J D The anomalous origin of the left coronary artery from the pulmonary artery Brit. Heart J 21 149 1959
9. Vince, D J and Keith, J D The electrocardiogram in ventricular septal defect, Circulation 23:225, 1961
10. Pileggi, F Bocanegra, J Tranchesi, J Macruz, R., Borges, S., Portugal, O Villarinho, M G Barbato, E. and Decourt, L. V The electrocardiogram in tetralogy of Fallot a study of 142 cases, Am. Heart J 59:667 1960
11. Astley R., Oldham, J S., and Parsons, C. Congenital tricuspid atresia, Brit. Heart J 15:287 1953.
12. Brown, J W Heath, D and Morris, T L. Tricuspid atresia, Brit. Heart J 18:499 1956.
13. Anderson, R. C., Lillehei, C. W and Lester R. G.: Corrected transposition of the great vessels of the heart, Pediatrics 20:626, 1957

Table IV Criteria of left ventricular diastolic overloading in ventricular septal defect

Number of cases	Pulmonary to systemic flow ratio	Right ventricular pressure (mm. Hg)	Average size (mm.)		
			Q_V	R_{V_6}	T_V
8	1-2	>90	0.6	10	3.4
37	1-2	<90	2.9	16	3.3
23	2-3	Only 4 patients in these groups had a right ventricular pressure over 90 mm. Hg hence these groups were not subdivided	2.0	15	1.9
17	3-4		2.7	17	2.7
27	4 or more		3.7	21	3.0

condition the ventricles are transposed. If there were also transposition of the ventricular conduction system this would explain the usual absence of a Q_{V_6} in this condition as noted in our cases and by other observers[13] and it would also explain why a Q wave is usually seen in Lead V_1.

Discussion

A review of the electrocardiographic findings in our case material confirms the concept that a deep Q wave in the left precordial leads is one of the features of left ventricular diastolic overloading. Furthermore, it is the most frequent single indication of left ventricular diastolic overloading, and a change in the depth of Q_{V_6} is a most useful indication of a *change in left ventricular diastolic overloading.* Tall peaked T waves have been referred to as indicative of such an overload. We have found the Q in Lead V_6 to be more characteristic. Furthermore, tall peaked T waves were frequently not noted even in the presence of clear evidence of left ventricular diastolic overload.

We compared three electrocardiographic features (depth of Q, height of R, and height of T, all in Lead V_6) as indicators of left ventricular diastolic overload in patent ductus arteriosus and ventricular septal defect. In patent ductus arteriosus the postoperative change in hemodynamics was best reflected by Q_{V_6} rather than by R_{V_6} or T_{V_6} (see Table III). However, in the subgroups of ventricular septal defect the correlation of flow ratios with the R wave in Lead V_6 was more consistent than with the Q wave in Lead V_6, even if full allowance were made for those cases of right ventricular hypertension and relatively little left-to-right shunt. Both correlated better than did the T wave in Lead V_6. The amplitude of R_{V_6} increases in both left ventricular systolic overloading and diastolic overloading, whereas Q_{V_6} is either normal or diminished in left ventricular systolic overloading. Thus a deep Q_{V_6} is more specific for diastolic overloading (see Table IV).

Other conditions which produce a deep Q_{V_6} include hypertrophy of the left ventricular portion of the septum and myocardial injury. The ventricular complexes of myocardial injury differ from those of left ventricular diastolic overloading in that they feature a small or absent R wave, a delayed intrinsicoid deflection, and often characteristic S-T-segment and T wave changes.

Summary

The electrocardiograms of nearly one thousand patients with congenital heart disease were studied with particular reference to the Q wave in Lead V_6. (1) Patients with left ventricular diastolic overloading, especially when it was associated with a left-to-right shunt, developed a deep Q_{V_6}. (2) If the degree of diastolic overloading changed, the depth of Q_{V_6} changed correspondingly (e.g., ligation of a patent ductus reduced the size of Q_{V_6}). (3) The depth of Q_{V_6} was the most useful single indicator of left ventricular diastolic overloading. (4) Patients who had ventricular

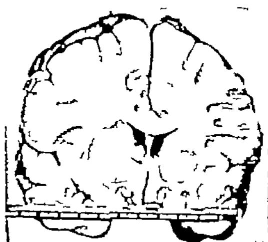


Fig. 1 Coronal section of the brain of the mother showing periventricular nodules of "candle guttering" type.

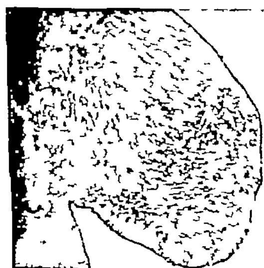


Fig. 2. Low-power microscopic view of a periventricular nodule in the brain of the mother showing predominating giant astrocytic hyperplasia.

microns in diameter (Fig. 5). Similar cells tended to lie free elsewhere in alveoli of the fixed lung. A small benign cortical fibroma was found in the left kidney and single multinucleated bizarre giant cell was detected in a capillary loop of one glomerulus. The site of uterine tearing was unremarkable.

The infant, on autopsy, showed bilateral lacerations of the tentorium, with intracerebral hemorrhage. Grossly and on microscopic study no signs of tuberous sclerosis were found in the brain. The only other change was the presence of multiple, apparently independent, nodules of pinkish-white tissue which measured up to 6 mm. in diameter; these were scattered throughout the

but tended to follow the epicardial distribution of the coronary arteries. A few nodules were noted beneath the endocardium and in the wall of both auricles (Figs. 6 and 7). Microscopically each nodule showed the clear-cut appearance which has been described as "congenital primary rhabdomyoma of heart" (Figs. 8, 9 and 10). No other lesions were detected. The family history was unobtainable.

Discussion

The normal characteristics of the three types of specialized cells of the subendocardial Purkinje network in human beings have been described by Obermeier[3] and later confirmed by Kugler and Parkin.[4] All are syncytial strap cells with peripheral striated myofibrils, central round nuclei which contrast with smaller oval myocardial nuclei and no intercalated discs.

The Type 1 cell is three to five times the diameter of a normal myocardial fiber often binucleated or quadrinucleated, and joins *only* with Type 2 the most common Purkinje cell. This cell is about twice the diameter of a myocardial fiber with soli-



Fig. 3. High-power ... showing a feltwork of giant ... fied microspherules (... of ...



Fig. 4. Lung of the mother, containing an angioma-like villous disorganization of the capillaries with adjacent normal lung. Low-power microscopic view.

tary central nuclei attached to occasional myofibrils which when seen in end view give an appearance which Ziehfeldt[8] described as "a spider hanging in a net." With hematoxylin and eosin staining the central fibril-free zone is empty looking but with special staining it contains a rich supply of glycogen. Transition into Type 3 Purkinje fibers is usual. This type of cell is only slightly thicker than a normal myocardial fiber but retains its spherical nuclei and tends to be found deepest in the normal myocardium. Intercalated discs are occasionally present at the points of junction with the myocardium. *Abrupt* syncytial transition of Type 2 directly into myocardial fibers by sudden convergence of myofibrils may occur uncommonly.

The normal human Purkinje fiber illustrated by Ham and Leeson[6] shows all the features of our Fig. 10. The close microscopic similarities of all the types of Purkinje cells with those occurring in so-called cardiac rhabdomyoma are obvious (see Figs. 8-10). In our case the monster cells are two to five times any comparative linear size of normal fibers of the Purkinje network seen in the same heart.

Since the first report, attention has been focused upon the vacuoles of these giant cells. Their empty appearance misled von Recklinghausen[3] to suppose that they were lymphangiomatous. Later, Virchow[7] was certain that the tumor arose from hyperplasia of the myocardium, and Marchand and Askanazy[8] demonstrated its glycogen content. This produced confusion subsequently with the diffuse cardiomegaly of glycogen-storage disease,[9] and the term "congenital glycogenic tumor" was coined,[10] implying a localized form of von Gierke's disease.[11]

Steinbiss[12] noted observations which tended to identify the rhabdomyoma cells by origin with embryonic myocardium or by differentiation with the type of conducting system cells seen most clearly in hoofed animals. He added that



Fig. 5. High-power microscopic view of a lesion in the lung of the mother. Note the multinucleated giant cell (magnification × 400).

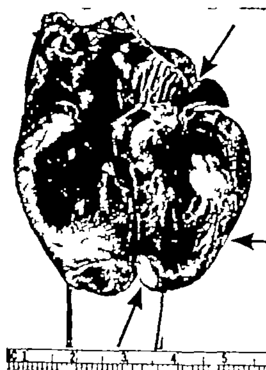


Fig. 6. Heart of newborn infant, showing intramural nodules in left ventricle, largely sparing the subendocardium, and in left auricle (*arrows*).

identification with Purkinje cells was very tempting but decided against it for they occurred independently of the conducting system and did not appear to produce heart block clinically. His final difficulty was failure to trace a gradual transformation between normal heart muscle fibers and most of the so-called neoplastic rhabdomyocytes. However, this imitates the *normal* absence of such transition except with Type 3 Purkinje cells, which, in any case, is characteristically abrupt. He finally regarded the rich glycogen content of the cells as some pathologic change similar to that which he also found in the periventricular tuberous nodules of the brain. (Strongly periodic-acid Schiff-positive granules occurred selectively in the cytoplasm of the giant astrocytes of the nodules in the brain of the mother in our report. They were only slightly water-soluble but were rapidly removed by diastase digestion.)

As a result, Seiffert and Kolisko's view[11] that because the cells were syncytial they must be a form of embryonic myoblast, held sway. However, the gigantism remained unexplained.

Some authors[12] have reported difficulty in showing glycogen in these giant myocardial cells. Beard and co-workers,[14] in a histochemical study on formalin-stored tissue from one case, showed that the periodic-acid Schiff-positive material was almost all freely soluble in water. The scant remainder was removable by diastase digestion.

We have repeated and do confirm Beard's observations. In addition, our tissue after storage for several months in formalin showed that periodic-acid Schiff-positive material remained only in close association with the myofibrils, but no longer in the vacuoles. With diastase digestion, even this was removed. We agree with Beard that the periodic-acid Schiff reactive material is presumably polysaccharide and *not* simple glycogen. The latter should fix adequately in aqueous formalin.[15] In this regard it is interesting that glycogen of von Gierke's disease is not recorded as highly water-soluble.[16] This metabolic disorder also does not produce *nodular* cardiac hypertrophy; thus, the older nomenclature "glycogenic tumor of heart," which implies a localized form of von Gierke's disease, no longer has precise scientific meaning.

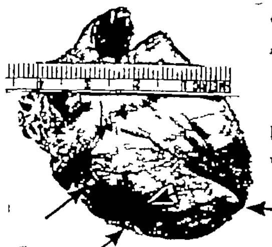


Fig. 7. Posterior surface of the heart of newborn infant, showing fine subepicardial nodules studding the course of the posterolateral coronary artery branch (*arrows*).



Fig. 8 So-called cardiac rhabdomyoma of newborn infant, showing a monster form of Purkinje fiber Type 1. The central cell shows characteristic double round nuclei and syncytial streaming of myofibrils (magnification × 1,000).

The multiple independent rhabdomyoma nodules of the myocardium have never been reported as precursors of invasive growth or metastasis. The two cases of true invasive cardiac rhabdomyosarcoma in infancy found in the literature[14] were both unicentric and not similar in histologic appearance to so-called cardiac rhabdomyomas. It has been well recognized that the latter are not neoplastic,[11, 17, 21] although their exact nature remained obscure. Steinbiss[23] noted that the natural history of nodules was cessation of growth and slow substitution by connective tissue even with calcification.[24] He stressed that the process was usually part of a common disturbance of the development of many types of cells in different organs which we include under the most recognizable clinical form as tuberous sclerosis. All 6 of his cases occurred in conjunction with this disorder. Farber[22] noted that of 32 cases in which the brain was described, in no fewer than 25 was there tuberous sclerosis. Willis[11] states: "It is probable that a more thorough examination of the brain and other organs would establish that all or nearly all cases of cardiac rhabdomyomata are indeed cases of tuberose sclerosis." He noted that this condition has been identified in more than half the recorded instances of cardiac rhabdomyoma and in all with many myocardial lesions. One can say that its existence as an independent entity has not been established.

Critchley and Earl[17] stressed the difficulty in detecting tuberous sclerosis as forme fruste and in infancy. For example, no record was available to them of the cerebral findings in any case of apparently isolated adenoma sebaceum. We have found only one brief note in the literature; this was by Byers,[7] who cited a case in which this apparently isolated skin condition in infancy was followed years later



Fig. 9. So-called cardiac rhabdomyoma of newborn infant showing giant Purkinje fiber Type 2. There is less sarcoplasm than in Type 1, the nuclei are single, and myofibrils occupy the periphery. No intercalated discs are present (magnification × 1,000).



Fig *10* So-called cardiac rhabdomyoma of newborn infant. Giant Purkinje fiber Type 3, showing abrupt transitions into ordinary myocardial fibers; their oval nuclei contrast with the round Purkinje type (magnification × 1 000).

by periventricular tuberous lesions. There is evidence that the abnormal process in cerebral tuberous sclerosis begins histologically around the end of the third month of fetal life.[18]

Although resemblance of "rhabdomyoma" to embryonic myocardium was noted by Marchand and Askanazy [8] and to Purkinje cells by Steinbiss [12] the latter was puzzled by the localization of intracardiac nodules "where fibers of the conducting mechanism are not present at all." In an excellent commentary Farber[14] pointed out that electrocardiography would not be available for study of this point in the majority of the first cases reported Certainly in his case and in that of Wegman and Egbert [16] intraventricular conduction defects were present. It would seem likely therefore, that there are *some* points of contact with the conducting bundle and the Purkinje network system This contrasts with diffuse cardiac glycogen-storage disease in which conduction defects appear to be the rule.[17]

However the hyperplastic process is not patchy hyperplasia of a maturing impulse-conducting system. There is little evidence that the nodules themselves form part of a functional network. Indeed many cases of so-called cardiac rhabdomyoma of multifocal type have been described in fetal life before the normal conduction network has fully appeared A search of the serial blocks of the heart of our infant indicated that an apparently intact normal-sized newborn Purkinje system beneath the endocardium (Fig 11) touched giant cells of the nodules on occasion but did not fuse with them. In addition occasional isolated giant Purkinje cells were seen lying in otherwise normal deep myocardial fiber bundles. This feature has also been remarked upon by Bigelow and co-workers.[18] Steinbiss[12] reported finding a few apparently normal heart muscle



Fig. *11* Left ventricle of the heart of newborn infant, showing the developing regular subendocardial conducting system, separated from myocardium from nodule of giant cells of so-called rhabdomyoma.



Fig. 8. So-called cardiac rhabdomyoma of newborn infant showing a monster form of Purkinje fiber Type 1. The central cell shows characteristic double round nuclei and syncytial streaming of myofibrils (magnification × 1,000).

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ology Washington, D C., 1956, Armed Forces Institute of Pathology fasc. 7 p. 14.

2 Von Recklinghausen, B.: Verhandl. d. Gesellsch. f Geburtsh 15 75 1863 Cited by Critchley and Earl.[17]

3 Obermeier O H F: De Filamentis Purkinjianis. Questio academica praemio coronata, In aug Diss., Berlin, 1866.

4. Kugler J G., and Parkin, J B Continuity of Purkinje fibres with cardiac muscle Anat Rec 126:355 1956.

5 Zechfeldt, W Cited by Steinbiss.[12]

6. Ham, A. W and Leeson, T S Histology ed. 4 Philadelphia 1961 J B Lippincott Company

7 Virchow R. Virchows Arch path Anat 30:468, 1864

8. Marchand, and Askanazy Verhandl d. deutsch path Gesellsch 3:64 1901

9 Putscher W Über angeborene Glykogenspeicherkrankheit der Herzens, Beitr z. path Anat. u.z. allg Path. 90:222, 1932.

10. Batchelor T and Maun, M Congenital glycogenic tumors of the heart, Arch Path 39:67 1945.

11 Humphreys, E. M and Kato, K. Glycogen storage disease thesaurismosis glycogenica (von Gierk) Am. J Path 10:589 1934.

12. Steinbiss, W Zur Kenntnis der Rhabdomyome des Herzens und Ihrer Beziehungen zur tuberösen Gehirnsklerose Virchows Arch path Anat 243:22, 1923

13. Hertzog, A. Congenital rhabdomyomatosis of the heart, Arch. Path 47 191 1949

14. Beaird, J Mowry R W and Cunningham, J A Congenital rhabdomyoma of the heart case report with histochemical study of tumor polysaccharide, Cancer 8:916, 1955

15 Vallance-Owen, J The histochemical demonstration of glycogen in necropsy material, J Path & Bact. 60:325 1948.

16. Engle M A. and Glenn F Primary malignant tumor of the heart in infancy case report and review of the subject, Pediatrics 15:562, 1955.

17 Critchley M., and Earl, C. J C Tuberous sclerosis and allied conditions, Brain 55:311 1932.

18. Rehder H Virchows Arch. path Anat. 217:174 1941

19 Crowell, W M and Rice, E. C. Congenital rhabdomyoma of the heart, Clin. Proc. Child Hosp., Washington 2:292, 1950.

20. Bigelow H H Klinger S., and Wright A W Primary tumors of the heart in infancy and early childhood, Cancer 7:549 1954

21 Taber R. E. and Lam C R. Diagnosis and surgical treatment of intracardiac myxoma and rhabdomyoma, J Thoracic Surg 40:337 1960

22. Farber S. Congenital rhabdomyoma of the heart, Am. J Path 7 105, 1931

23 Willis, R A. The borderland of embryology and pathology London, 1958, Butterworth & Company

24 Farber S. Clinical pathological conference, J Pediat 55:240 1959

25 Elliott G B and Wollin D G. Defect of the corpus callosum and congenital occlusion of fourth ventricle with tuberose sclerosis, Am J Roentgenol. 85 701 1961

26. Wegman M and Egbert, D Congenital rhabdomyoma of the heart associated with arrhythmia, J Pediat. 6:818, 1935

27 Johnson, F R Cardiac hypertrophy in infancy Pediat Clin. North America 1:235, 1954

28 Duckworth, J W A The development of the sino-atrial and atrio-ventricular nodes of the human heart M D thesis, 1952 University of Edinburgh

Experimental and laboratory reports

An anatomic and electrocardiographic study of the heart of the camel

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Our familiarity with the earlier studies of Braun Rosenberg and Bellini[1] on the camel heart induced us to carry out a similar investigation* at the end of our medical survey among the shepherds of Somaliland

Method and materials of study

The electrocardiographic studies were carried out on two young camels which were to be slaughtered in the abattoir of Mogadishu They weighed approximately 240 and 250 kilograms. For this registration we used a direct-writing portable electrocardiographic apparatus Galileo with two pens which had a standardization of 1 cm = 1 mv

The electrodes were 4 steel needles which we inserted 4 to 5 cm beneath the skin of the proximal parts of the animal's limbs The animals were forced to lie down but they were agitated and we had to tie them. We presume that they were disturbed by the presence of a large number of persons and by the odor of the blood of other camels which had already been slaughtered Moreover they were bothered by the unusual position we obliged them to stay in so that we could dispense with anesthesia

General description of the electrocardiographic tracings (*Fig 1*) We used the peripheral and unipolar leads of the extremities D_1 D_2 D_3 aV_R aV_L and aV_F For obvious reasons chest leads could not be used

The tracings in sinus rhythm showed a frequency of 60 per minute The P wave could be clearly distinguished with a maximal width of 0 10 second in Lead D_1 and a maximal height of 2 mm in Lead D_2. The P wave was positive in Leads D_1 D_2 D_3, aV_L aV_F and negative in Lead aV_R

The P-Q interval varied between 0.24 and 0 28 second and was always isoelectric. The maximum duration of the QRS complex was approximately 0 08 second with a maximum amplitude of the positive R wave of 11 mm. in Lead aV_L and with a maximum amplitude of the negative S wave of 16 mm in Lead D_3. The ventricular complex showed the Rs aspect in Lead D_1 RS in Lead D_2 rS in Lead D_3, Qr in Lead aV_R Rs in Lead aV_L, and RS in Lead aV_F

The S-T segment was always isoelectric The T wave had a maximum duration of 0 08 second and a maximum amplitude of 5 mm The T wave was negative in Leads

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*The present study was conducted while Lapiccirella group was carrying on an investigation in the Somali Republic, with the cooperation of the World Health Organization, on the nomadic shepherds whose diet consists exclusively of camel milk in large amounts. The study on the camels was made in the slaughterhouse of Mogadiscio, with the invaluable help of Dr. Carnello, Dr Lanciani, and Dr Venturini.

D_1, D_2, D_3, aV_F diphasic plus or minus in Lead aV_L, and positive in Lead aV_R. The Q-T interval oscillated between 0.36 and 0.40 second.

Anatomic research. Since it was impossible to carry out the anatomic and histologic examination on the spot, we fixed the hearts in formalin and took them home.

In Florence, the examination was carried out by Professor Fiorio of the Institute of Pathological Anatomy of the University of Florence. Since the findings were similar in the two cases, we present here only one description. (a) The hearts weighed 1,250 and 1,300 grams. (b) 48 histologic sections through the central part of the right atrioventricular fibrous ring were made. (c) 24 histologic sections on the right and on the left sides of the interventricular septum were made, and (d) 16 histologic sections below the aortic cusp nearest to the septum were made.

In spite of the small number of histologic sections, the myocardial fibers of the conduction system could be easily recognized because of their constant position, their dimensions, their shape and staining characteristics (little uptake of eosin: histochemical staining methods were not applied) and finally because they were accompanied by nerve branches without ganglia, distinctly visible in the Tawara-Aschoff node and, although very thin, still clearly recognizable along the branches of the bundle of His.

There were no topographical contacts to be observed with the fibers of the myocardium itself. This might suggest a direct continuity between the fibers on the two sides of the septum—at least in the central part. In the atrioventricular node, however, interposed folds of dense fibrous tissue were present, and even a spur of osseous tissue (*os cordis*), so that we could not be sure of similar topographical contact.

In the myocardial zone immediately below the aorta, one got the optic impression of a very distinct continuity of tissue between the Purkinje fibers, which were very large and swollen to the point of appearing empty, and the thin but structurally compact common myocardial fibers.

It was difficult to determine whether the fibers under study were in a normal condition or not. The fixation of the anatomic fragment was unavoidably imperfect and, because of their peculiar biochemical characteristics, the Purkinje fibers are obviously susceptible to extensive postmortem changes. These changes may be ascribed to excessive vacuolization and in the node of Tawara-Aschoff it is not uniform but involves the fibers to different degrees.

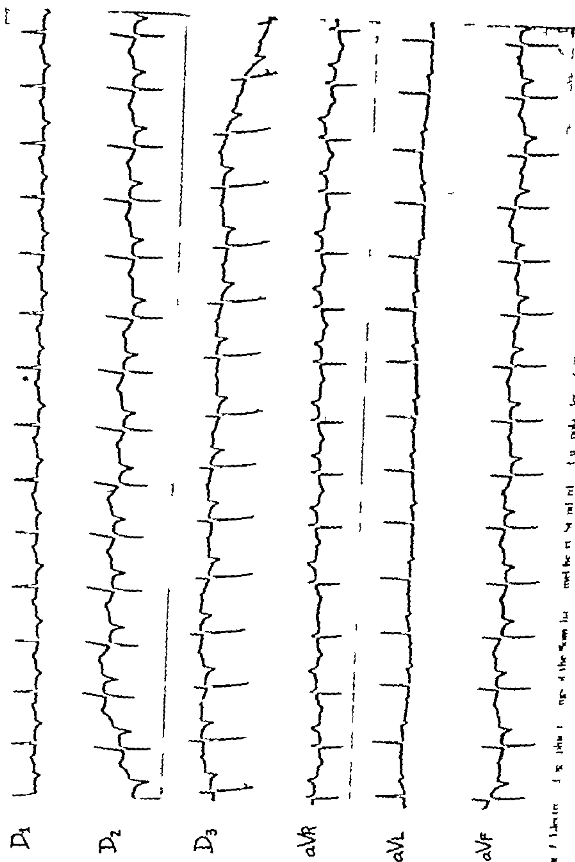
On the whole, the impression received was that the myocardium was in good condition since there were no microscopic cicatricial zones and the intracardiac arterial branches were intact. Some reservations are justified, however, in regard to the condition of some of the arterioles, because their muscular layer was sometimes irregularly thickened and not clearly structural in its components.

These phenomena can probably be ascribed to adaptation rather than to a dysmetabolic condition, and the same can be said about the findings of amorphous subendocardial pads at the places where a smaller branch grows out of a larger one.

For a more detailed study of the coronary circulation we asked Professor Giorgio Weber of the Institute of Pathological Anatomy of the University of Florence to carry out a specific examination of these arteries. He reported as follows:

Staining haematoxylin-eosin and Weigert for the elastic fibers was employed. The arteries examined showed no structural alterations of significance. There was no thickening of the intima or lesions of the media. The lamina elastica interna appeared to consist of lamellar structures that were lying close to each other but loose, not completely combined into a genuine membrane. Very clearly visible were the bundles of longitudinal muscular fibrocells around which could be observed neat "shells" of elastic fibrils. There were also more or less distinct connective-tissue areas. In some sections, the elastic structures of the media showed a few scattered very small circumscribed areas of rarefaction.

This examination was repeated by Professor Allara, Director of the Institute of Normal Histology of the University of


D1
D2
D3
aVR
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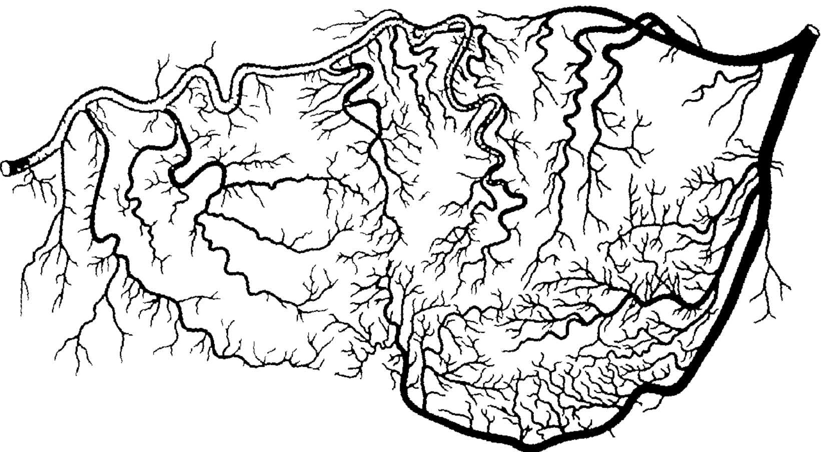


Fig. 2 Schematic representation of the coronary system of the Somalian camel heart (by Prof. M. Pasfani, of the Institute of Pathological Anatomy of the University of Florence, Florence, Italy). *Grey*: Left coronary artery. *Black*: Right coronary artery.

Florence who verbally reported analogous findings.

Fig 2 is a drawing of the coronary circulation of the camel made by Professor Manfredo Fanfani on the basis of his anatomic study of the two camel hearts.

Discussion

The assertion made half a century ago by F Buchanan and much later again by King Burwell and White[4] that the larger a heart is the slower will be its rhythm has been not confirmed by our results Also the later studies of White and Senft on the whale heart have shown that this statement does not always apply since an elephant heart which weighed 20 kilograms (?) was found to beat at the rate of 30 beats a minute whereas a whale heart which weighed 2 /2 kilograms had a rate of 15 beats a minute

The fact that we found in our animals a heartbeat twice as fast as that reported by Braun Rosenberg and Bellin[1] for the camels they examined is undoubtedly to be attributed to the circumstances of our investigation that is it had to be carried out in the abattoir of Mogadishu where the camels were already in a state of terror for the reasons already noted Instead Braun Rosenberg and Stern[2] carried out their hemodynamic tests – very remarkable indeed – with the animals under Pentothal anesthesia and we assume that the electrocardiographic examination was also carried out with the animals under Pentothal anesthesia This fact could explain the very markedly different findings in regard to cardiac frequency

The voltage of P-QRS-T might be defined on the whole as similar to that seen in the electrocardiogram of human beings. The Q T interval also in view of the frequency observed could be considered to be within the limits of electrocardiographic curves recorded in human beings.

These findings might indirectly support the comparability of our results with those of Braun Rosenberg and Bellin since according to the formula of Bazett a lengthening of the Q T interval always corresponds to a lower rhythmic frequency The P-Q interval as appears from the detailed description given above showed the same characteristics of lengthening that the earlier authors have described

It appears therefore that the only fixed element that we might regard as a species-specific anatomo-functional character is the lengthened interval of the atrioventricular conduction

To subject our camels to an effort test would have been not only superfluous in this connection but also futile in view of the almost continuous physical activity which has made the endurance of the camel a species trait

REFERENCES

1 Braun, K Rosenberg S. Z. and Bellin, L. The electrocardiogram of a camel, AM HEART J 55:754 1958.
2 Braun, K., Rosenberg S. Z., and Stern S. Some hemodynamic observations on a camel, AM HEART J 57:91 1959
3 Curasson, G. Le chameau et ses maladies, Paris, 1947 Vigot Frères Ed
4 King R L., Burwell, C S and White P D: Quoted by Braun, et al.
5 King R. L., Jenks, J L., and White P D: Quoted by Braun, et al.[1]
6. Senft A W and Kanwisher J K: Cardiographic observation on a finback whale Circulation Res. 7:961 1960
7 White P D., Jenks, J L. and Benedict F G: ECG of the elephant AM HEART J 16:744 1938.
8 White P D Matthews, S. W and Roberts, J B: Hunting the heartbeat of a whale National Geographic 110 49 1956.

Atrial parasystole with interpolation

Observations on prolonged sinoatrial conduction

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Both atrial parasystole[1,2] and interpolation of atrial premature systoles[1,3-11] are rare phenomena. In so far as we were able to ascertain, a combination of the two mechanisms, as revealed by the records to be described, has not been reported previously. In addition, our case provides a unique opportunity to determine the duration and localization of a simple delay in sinoatrial (S-A) conduction.

Analysis of electrocardiograms (*Figs. 1-4*). The electrocardiograms were obtained on a 79-year-old patient with arteriosclerotic heart disease. The records in Figs. 1 and 4 are parts of one electrocardiogram, and those in Figs. 2 and 3 are parts of another record taken 3 days later. The measurements (in 1/100 sec.) presented in Tables I through IV include portions of records not illustrated. A regular and undisturbed sinus rhythm (rate of 72) is present in Lead V_1 of Fig. 2; other records show premature P waves (labeled P') which differ in contour from the sinus P wave. Most of the P' waves are followed by a ventricular complex. However, among those which occur very early in the cycle, some are not conducted to the ventricles (Fig. 1 V_1, Fig. 2, II, III, aVF, Figs. 3 and 4) and others are associated with aberrant ventricular conduction (Fig. 1 V_4, Fig. 4 aVF). Two features of the atrial irregularity stand out (Table II): (a) the spacing of the premature ectopic P waves bears no fixed relationship to the preceding sinus P wave (i.e., the coupling of the ectopic P wave varies), and (b) short interectopic intervals (P'-P') are about equal (1.12 to 1.28 sec.), whereas long ones are simple multiples of the short ones (2×1.14 to 2×1.33 sec.). Thus, the spacing of the ectopic atrial beats fulfills the criteria for a parasystole, as established in the more common form of ventricular parasystole. Furthermore, absence of an expected ectopic P wave can always be accounted for by the shortness of the calculated "latent" coupling, i.e., physiologic refractoriness of the atrial muscle after activation by the sinus impulse (Table II). In short, we are dealing with an atrial parasystole (average rate of 50) with continuous protection of the parasystolic focus from the sinus impulse, and no evidence of an exit block of the ectopic impulse is present.

The measurements of all consecutive

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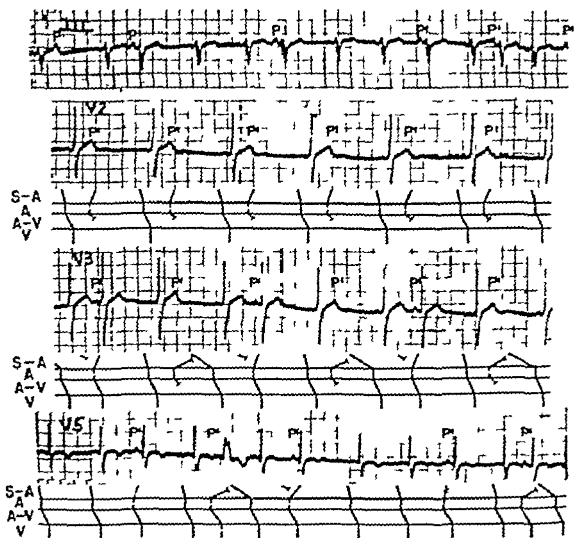


Fig. 1. *Lead III.* The coupling of the tall ectopic premature P waves (P′) varies. The two long interectopic intervals (P′-P′) in the middle portion of the record are about twice as long as the short ones at the beginning and end of the record. A sinus cycle (P-P) precedes and follows the third ectopic P wave. Note the variations in the duration of the returning cycle (P′-P): the second and third P′-P are longer than P-P, indicating discharge of the S-A node by the ectopic impulse; the first and last P′-P are shorter than P-P and indicate interpolation; and the fourth P′-P is about equal to P-P, indicating interference (full compensatory pause). See diagrams below Leads V, which indicate the three mechanisms. *Lead V₂,* Temporary allorhythmia (atrial bigeminy) with fixed coupling. Discussed in text. *Lead V₃,* Temporary Bradyrhythmia due to "interpolation" of every other ectopic P wave. The lengthening of the P-P cycle is explained by prolongation of the postectopic S-A conduction after interpolation. *Lead V₅,* Note the three mechanisms responsible for the varying duration of the returning cycle (P′-P): discharge of the S-A node by the ectopic impulse; "interpolation" of an early ectopic impulse; and interference between late ectopic and the S-A nodal impulse.

P-P intervals, regardless of P origin, are given in Table I; those intervals terminated by an ectopic P wave (P′) appear in boldface type. The figures listed in Table II are all derived from Table I and indicate the duration of: (a) the coupling of the ectopic beats (P-P′), (b) the returning cycle (P′-P), (c) the sinus cycle (P-P), (d) the interectopic interval (P′-P′), and (e) the calculated latent coupling. The duration of the returning cycle (P′-P) shows considerable variations. At first sight, one might ascribe these differences to a sinus arrhythmia, but such an interpretation is precluded by the regularity of the sinus beats in the portion of the

record undisturbed by premature beats (Fig 2 V_4) and by the absence of marked variations in the duration of single sinus intervals in the same record (Table II P P) In Table III data taken from Table I are arranged in an order which permits examination of the relationship of the duration of the returning cycle (P' P) to the prematurity of the manifest ectopic impulse (P P')

Retrograde conduction time and depressant effect of premature ectopic impulses The majority of the ectopic impulses, viz. those that do not occur very early or very late in the sinus cycle, are followed by a returning cycle (P' P) which as expected exceeds the duration of the measurable sinus cycle (P P) (Table II) This indicates discharge of the S-A pacemaker by the ectopic impulse. The varying duration of the returning cycle is determined primarily by two factors (a) the time required to reach the pacemaker (A S conduction)[2] and (b) the depressant effect of the premature discharge on the rate of impulse formation in the pacemaker[12] The contribution of each of these two factors cannot be separated Hence the retrograde conduction time from the ectopic pacemaker to the S-A node cannot be determined with accuracy Disregarding the depressant effect of the premature ectopic impulse retrograde conduction time was estimated to increase up to 0 10 sec[1] or 0 24 sec.[2]

Although A-S conduction would tend to be longer when the ectopic impulse occurs earlier and the depressant effect would tend to be more marked the earlier the pacemaker is discharged actually the two effects tend to neutralize each other since slower A-S conduction will



Fig 2 *Lead* I Regular undisturbed sinus rhythm. *Lead* II The impulse of the first P' occurs lat[illegible] and [illegible] interferes with the S-A nodal impulse (full compensatory pause) the second P' occurs early and [illegible] interpolated (returning [illegible] le shorter than P P) the impulse of the third and fourth P' occurs later and discharges the S-A node (returning [illegible] le longer than P P). *Lead III* Note that the first ectopic impulse discharges the S-A node (long P' P) although it occurs earlier than the impulse of the third P' which fails to reach the S-A node and is interpolated Discussed [illegible] text *Leads II* and [illegible] The pattern of the atrial arrhythmia is [illegible] A[illegible] rhythmia (atrial bigeminy) with fixed coupling is prevented because the third ectopic impulse falls into the refractory period of the atrial muscle (latent coupling 0 30 sec) and fails to elicit [illegible] response

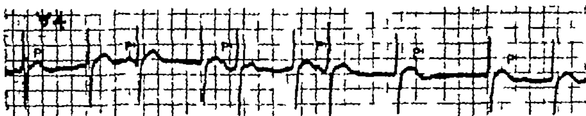


Fig. 3. Atrial parasystole giving rise to atrial bigeminy. Variations in the returning cycle (P′-P) are responsible for the variations in coupling (cf. Lead V in Fig. 1).

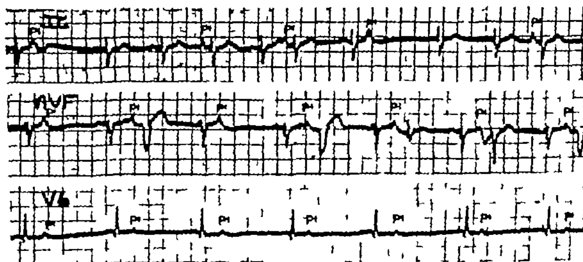


Fig. 4. *Lead II.* The returning cycle (P′-P) after the second and last P′ is 0.10 sec. shorter than the preceding sinus cycle (P-P). Since interpolation is unlikely in view of the late occurrence of P′, this suggests interference with the sinus impulse following acceleration of the S-A pacemaker after temporary depression due to premature discharge by the preceding parasystolic impulse. *Leads aVF and V6.* These show continuous atrial bigeminy. In Lead aVF the ectopic P waves with the shortest coupling (first and third P′) are nonconducted; the others are followed by aberrant ventricular conduction. In Lead V6 there is an alternation in the duration of the coupling in that a shorter coupling is associated with a shorter returning cycle. Discussed in text.

delay the discharge and thus decrease the depressant effect. On the other hand, a supernormal phase of conduction of the early ectopic impulse could lead to shortening of the returning cycle if faster A-S conduction outweighs the more marked depression which follows the earlier impulse. Such a state is actually suggested by the findings in Lead III of Fig. 2, where the P-P′ associated with discharge of the S-A node is shorter than the P-P′ associated with interpolation, and by the findings in Lead V_6 of Fig. 4, where the shorter P-P′ intervals are followed by the shorter P-P intervals. Furthermore, marked lengthening of the returning cycle may occur after a late P′ if the latter follows pseudointerpolation (see below) (Fig. 1, V_3). Here the increase of P′-P can be expected as a result of slow A-S conduction rather than of a depression by the ectopic impulse. In view of the complex interrelationship of these factors, it is not surprising that the delaying effects of the premature ectopic impulses cannot be predicted (Table III).

Interpolation of atrial premature systoles. Tables I and II reveal the presence of returning cycles which are considerably shorter than the measurable sinus cycle (P-P) in the same record and which occur exclusively after ectopic beats with a short coupling (Fig. 1, Lead III after the first and penultimate P′, V_2 after the second, fourth, and sixth P′, V_3 after the second and last P′; Fig. 2, V_{3R} after the second P′, III after the third P′; Fig. 3, after the first and last P′). These short returning cycles

can be accounted for by failure of the early ectopic impulse to reach and discharge the site of impulse formation in the sinus node (presumably because of refractoriness of A-S conducting tissues) followed by delayed conduction of the next sinus impulse as a result of some refractoriness of the same tissues now being used for S-A conduction. This interpretation is based on the analogy with the familiar phenomenon of delayed A-V conduction after interpolation of ventricular premature systoles. Evidently the difference between the normal atrial cycle (P-P) and that which includes an interpolated atrial premature systole (P-P′-P) represents the delay in S-A conduction of the postectopic sinus impulse (see diagrams in Fig. 1, V_1 and V_4). Of 12 interpolated atrial premature systoles (Table IV) 4 are conducted to the ventricles, one of them (Fig. 1, second P′ in V_4) with aberrant conduction. Actually, as the diagrams in Fig. 1 indicate, the interpolation is a pseudointerpolation inasmuch as it can be shown that the next sinus impulse is blocked rather than interfered with. A "postponed compensatory pause"[14] does not occur because of the timing of the next ectopic P wave (P′). Blockage of the sinus impulse which follows the "interpolation" has to be postulated in view of the long duration of the following P′-P interval which indicates that the impulse of P′ had reached the sinus node. Table IV shows that the delay of S-A conduction of the postectopic beat amounts to 0.08 to 0.34 sec. It is in a range similar to the prolongation of A-V conduction after interpolation of ventricular premature systoles.

Just as the postectopic prolongation of A-V conduction after interpolated ventricular premature systoles is explained as a result of concealed retrograde conduction in the A-V junction,[14] so the postectopic prolongation of S-A conduction after interpolated atrial premature systoles represents evidence—the first—of concealed A-S conduction.

Atrial premature systoles with fully compensatory pause. Appreciable lengthening of the returning cycle over the simple sinus P-P does not occur after very late ectopic beats (Tables I and III; Fig. 1, fourth ectopic P in III and penultimate P′ in V_4; Fig. 2, first P′ in V_{2R}, second P′ in III, and third P′ in aV_F). Actually, slight shortening of P′-P may occur (Fig. 4, second and last P′ in II) and this can be explained as only an apparent shortening, since the preceding measurable sinus cycle (P-P) is still prolonged as a result of a temporary depression of the S-A node (see above). Again, it would appear that the ectopic impulse fails to reach the sinus node—this time, not because of refractoriness of the tissues of A-S conduction but because of physiologic interference with the impulse of the sinus pacemaker shortly after its spontaneous discharge. This results in a fully compensatory pause. Fusion P waves were not observed.

On occasion, the mechanism that determines the duration of the returning cycle cannot be definitely identified on account of the interplay of arrhythmia of the sinus pacemaker, variations in conduction time, and the depressant effect of the premature ectopic impulse (Table IV).

Refractory period of the atrial muscle and of the S-A nodal tissue. The duration of refractoriness of the atrial muscle, i.e., the time when it fails to respond to the parasystolic impulse after a response to the sinus impulse, can be delineated by determining the longest latent and/or the shortest manifest coupling of the parasystolic atrial beat. In our case (Table II) the longest latent coupling measured 0.34 sec., the shortest manifest coupling 0.36 sec. The latter value is intermediate between the shortest duration of 0.26 sec. found in the well-documented atrial parasystole of Jervell[3] and the value of 0.40 sec. or more obtained in cases of A-V nodal parasystole with retrograde conduction.[15] This is not surprising since the shortest P-P′ intervals in the latter cases actually are determined by the refractory period of the A-V nodal tissues and not by that of the atrial muscle.

Obviously, interpolation of atrial premature beats presupposes failure of the S-A pacemaker tissue to be discharged by the ectopic impulse. Since the contour of the interpolated P waves tends to be identical with that of the other ectopic P waves, occurring later in the cycle, the intra-atrial spread of the ectopic impulse

Table I. Consecutive atrial intervals (in 1/100 sec.)

Fig. 1													
III	38	64	32	90	74	54	82	68	68	68	44	54	62
V	[illegible]	78	[illegible]	78	[illegible]	8	12	78	12	84	36	80	
V	48	86	38	64	54	86	36	66	58	86	36	70	
V	90	68	80	36	68	58	92	6	72	78	48	56	
Fig. 4													
II	36	90	78	68	68	16	80	38	88	80	64	70	
aVF	38	78	44	84	39	80	42	82	40	82	40	[illegible]	42
V	44	86	40	80	44	84	38	78	46	8	39	80	44
aVR	4	10	76	42	84	8	68	2					
V	44	80	40	80	[illegible]	8	42	78					
V	90	74	70	2	48	6	46	90	80	68	6		
Fig. 2													
V	80	78	80	88	66	88	96	80	60	96			
II	44	92	40	100	92	68	92	38	92	44			
III	36	98	90	78	84	46	62	8	100	84			
aVF	36	94	40	100	88	72	86	40	88	48	90		
V	84	82	82	84	82	82	82	82	[illegible]				
Fig. 3													
V	36	54	68	92	40	88	44	96	38	92	42	48	
I	36	90	40	100	90	38	82	46	88	94	60		
V	48	94	94	62	100	82	66	96	82				
aVL	36	90	46	100	88	62	92	82	78	82			
V	80	48	82	46	90	40	98	94	68	96			
V	86	80	20	92	38	90	[illegible]	46	72	88	80	80	
V	52	98	86	62	94	82	72	90					

[illegible] initiated by an ectopic P wave (P') are shown in boldface type.

must remain the same. It would appear that response to conduction of the ectopic atrial impulse toward the pacemaker (A-S conduction) fails in the same tissues which respond with delay in conducting the sinus impulse (S-A conduction) after interpolation. Since such delay can be localized best within the S-A nodal tissues (see below), the coupling of the interpolated parasystolic beats (Table IV) most likely delineates the refractory period of a portion of the S-A nodal tissues. The refractory period of the S-A pacemaker is expected to be longer than that of the atrial muscle.[17] In our case, the refractory period of S-A nodal tissue gauged by the duration of the coupling of interpolated atrial beats shows considerable variations (0.36 to 0.48 sec., cf. Fig. 2, Lead III, first and third P') possibly due to the operation of a supernormal phase.

The coupling in atrial parasystole. Varying coupling of the ectopic beats, the earmark of a ventricular or A-V nodal parasystole without retrograde conduction to the dominant pacemaker, is not to be expected in atrial parasystole provided that the rates of both the sinus node and the ectopic pacemaker are precisely regular and conduction from the ectopic pacemaker is constant. Under such circumstances a regular irregularity (allorhythmia) with fixed coupling should develop as a result of discharge at a constant interval of the dominant pacemaker by the premature impulse.[1] However, even slight irregularity of the sinus or ectopic pacemaker or varying conduction from the latter may prevent the discharge of the sinus node because of refractoriness of the atria or of the conducting tissues between the ectopic pacemaker and the site of impulse formation in the sinus node, thus leading to marked variations in the coupling of subsequent ectopic beats. In one of the tracings in our case the coupling of the ectopic beats is fixed and the atrial rhythm presents a regular irregularity

(Fig 1 V4) in the other tracings absence of atrial activation by the parasystolic impulse or interpolation of the ectopic impulse are followed by marked changes in the coupling of the subsequent ectopic beats.

Site and nature of S-A block In clinical electrocardiography there are two conditions in which a delay in the occurrence of the sinus P wave suggests a delay of S-A conduction (a) atrial premature systoles with marked prolongation of the returning cycle and (b) second-degree S-A block with evidence of Wenckebach periods of S-A conduction.[19] Our case of interpolated atrial premature systoles in the presence of a rather regular sinus pacemaker provides a new opportunity to gauge the increase in S-A conduction time from one beat to another By analogy with the events which follow interpolation of ventricular premature systoles the postextrasystolic prolongation of conduction can be determined by comparing the P P intervals which contain interpolated beats with the normal sinus cycle (Table IV) Such postextrasystolic prolongation of S-A conduction has not been observed in clinical cases of interpolated atrial premature systoles but is suggested by the experimental data of Drury and Brow [17] Its occurrence in our case indicates the presence of a latent depression in S-A conduction

In spite of many clinical observations on S-A block and attempts to study S-A block in the experimental animal the site of blockage of S-A nodal impulses which

Table II Rearranged measurements derived from Table I and calculated latent coupling

	Coupling, P P' (1/100 sec)	Returning cycle P' P (1/100 sec)	Sinus cycle P P (1/100 sec)	Interectopic interval P' P' (1/100 sec)	Latent coupling P P' (1/100 sec)
Fig. 1					
III	38 52 54 68 44 62	64 90 82 68 84	74 68	116 218 218 112 116	19 26
V	42 42 42 42 42 36	78 78 78 78 84 80		120 120 120 120 120	
V[illegible]	48 38 58 36 58 36	86 64 86 66 86 70		124 122 122 124 122	
V	68 36 58 72 42	80 66 92 78 86	80 76	116 126 240 120	28 28
Fig. 4					
II	36 68 46 38 64	90 68 80 88 70	78 80	236 114 118 232	28 28
aVF	38 44 39 42 40 40 42	78 84 80 82 82 82		122 123 122 122 124	
V	44 40 44 38 46 39 44	86 80 84 78 82 80		128 126 124 126 122 122	
V[illegible]	40 42 68	74 76 78 72	78	114 118 230	28
V[illegible]	44 40 42 42	80 80 78 78		120 122 120 120	
V	70 48 46 68	90 72 76 90 76	74 80	234 120 122 238	28
Fig 2					
V[illegible]	78 48 58 60	80 66 96 96	80 80	128 124 236	22 25 25
II	44 40 68 38 44	92 100 92 92	92	132 260 130 136	30
III	36 78 46 70	98 84 62 100	90 84	266 130 132	32 32
aVF	36 40 72 40 48	94 100 88 86 90	88	134 260 128 134	30
V			84 82 82 84		
V			82 82 82 82 82		
Fig 3					
V	36 68 40 44 38 42	84 92 88 96 92 48		122 132 132 134 134	
aVR	48 62 66	94 100 96	94 82 82	250 248	30 24 30
V[illegible]	36 46 62 78	90 100 92 82	88 82	136 250 252	22
V	48 46 40 60	80 82 90 98 96	94	128 128 130 252	32 32
V	46 50 38 42 72 80	80 92 90 46 88	80	130 130 132 118 248	34
V	32 62 72	98 94 90	86 82	246 248	26 30

The P'-P values shown in boldface type indicate interpolation of the ectopic impulse.

Table III Relationship between duration of coupling of ectopic atrial beat (P P') and duration of returning cycle (P' P)

	P P' P' P (1/100 sec)	Mechanism
Fig 1		
III	38 – 64	Interpolation
	44 54	
	52 – 90	Discharge of S-A node
	54 82	
	68 – 68	Interference
V	36 – 80	
	42 – 78	Discharge of S-A node
	42 84	
V	36 70	
	36 66	Interpolation
	38 64	
	48 86	
	58 86	Discharge of S-A node
	58 – 86	
V	36 68	Interpolation
	42 56	
	58 – 92	Discharge of S-A node
	68 80	
	72 78	Interference
Fig 4		
II	36 90	
	38 88	Discharge of S-A node
	46 80	
	64 70	Interference
	68 – 68	
aV	38 78	
	39 80	
	40 82	
	40 82	
	42 82	
	44 – 84	
V	38 78	Discharge of S-A node
	39 80	
	40 – 80	
	44 – 86	
	44 – 84	
	46 82	
aVR	40 – 76	
	42 – 84	
	68 72	Interference ?
Vm	40 – 80	
	42 76	
	42 – 78	Discharge of S-A node
	44 – 80	
V	46 90	
	48 – 76	
	68 – 76	Interference ?
	70 – 72	Interference

	P P' P' P (1/100 sec)	Mechanism
Fig 2		
Vm	48 66	Interpolation
	58 – 96	Discharge of S-A node
	60 96	
	78 – 80	Interference
II	38 92	
	40 – 100	Discharge of S-A node
	44 – 92	
	68 92	Interference ?
III	36 98	Discharge of S-A node
	46 – 62	Interpolation
	70 – 100	Discharge of S-A node
	78 84	Interference
aVr	36 94	
	40 100	Discharge of S-A node
	40 88	
	48 90	
	72 86	Interference
Fig 3		
V	36 54	Interpolation
	38 92	Discharge of S-A node
	40 88	
	42 48	Interpolation
	44 96	
	68 92	
aVR	48 94	
	62 100	Discharge of S-A node
	66 96	
aVL	36 – 90	
	46 100	
	62 92	
	78 84	Interference
V	40 98	
	46 – 90	
	48 82	Discharge of S-A node
	60 – 96	
V	38 – 90	
	42 – 46	Interpolation
	46 – 80	Discharge of S-A node
	50 – 92	
	72 – 88	Interference
V	52 – 98	Discharge of S-A node
	62 – 94	
	72 – 90	Interference ?

fail to elicit an atrial response has not been determined In some cases of S-A block the spacing of the P waves indicative of Wenckebach periods of conduction would point to a localized disturbance of conduction in the presence of regular impulse formation Similarly the present observations tend to indicate a well localized disturbance which suggests that the same tissues which propagated the ectopic atrial

impulse toward the site of dominant impulse formation—without its actually reaching the pacemaker—were again traversed by the subsequent sinus impulse and were responsible for its delay. Thus, the new analogy between disturbed S-A and A-V conduction lends new support to the concept that places the conduction disturbance within the structure of the S-A node.[19] However, one has to assume a path within the structure of the S-A node along which the impulses have to travel before they spread in all directions along *connecting atrial fibers. Furthermore, in* our case the delayed P waves which follow interpolation of the ectopic beat do not differ in contour from the other sinus P waves. The absence of aberrant intra-atrial conduction after interpolation would seem to substantiate the assumption that the delay occurs within the tissues of the S-A node. Possibly, aberration does occur after interpolation in some cases of atrial premature systoles, but interpolation then can no *longer be diagnosed with certainty* since the result could not be definitely distinguished from multiple premature systoles.

Newer experimental techniques with microelectrodes and direct recording from the conducting tissues employed so successfully for the elucidation of disturbances of A-V and intraventricular conduction can be expected to shed new light on the spread of the impulse in the atria and on the site and nature of the disturbance referred to as sinoatrial block.

Summary

1. We have reported an unusual case of sinus rhythm with atrial premature systoles due to an independent ectopic pacemaker (atrial parasystole).

2. Marked variations in the duration of the returning cycle (P' P) after the ectopic atrial beats in spite of a fairly regular rate of the sinus pacemaker are accounted for in the following manner: (a) A P' P interval longer than the P P cycle indicates discharge of the sinus pacemaker by the ectopic impulse. This is seen with P' occurring *in the middle portion of* the cycle. (b) P' P intervals about equal to the P P cycle indicate interference of the ectopic with the next sinus impulse (fully compensatory pause). This is seen with P' occurring late in the cycle. (c) P' P intervals shorter than the P P cycle indicate interpolation of P' with postextrasystolic prolongation of S-A conduction time. This is seen with P' occurring early in the cycle.

3. *Events subsequent to interpolation* of the ectopic atrial impulse indicate that the sinus impulse which follows the post extrasystolic sinus impulse is blocked rather than interfered with. Thus the mechanism is that of a pseudointerpolation with postponed compensatory pause analogous to the same phenomenon which occurs after nodal or ventricular premature systoles.

4. Comparison of a single atrial cycle (P P) with one which contains an interpolated atrial premature systole (P P' P)

Table IV. Delay in S-A conduction after "interpolation" of ectopic atrial beat (P')

	Sinus cycle P P (1/100 sec.)	*Sinus cycle with "interpolated" ectopic beat P P' P (1/100 sec.)*	*Increase in postectopic S-A conduction time (sec.)*
Fig. 1			
III	74 68	102 (38+64), 98 (44+54)	0 24 – 0 34
V	?	106 (36+70), 102 (36+66), 102 (38+64)	?
V	80 76	104 (36+68), 98 (42+56)	0 18 – 0 28
Fig. 2			
Vm	80, 80	114 (48+66)	0 34
III	90 84	108 (46+62)	0 18 – 0 24
Fig. 3			
V	?	90 (36+54), 90 (42+48)	?
V	80	88 (42+46)	0 08

permits determination of the delay in S-A conduction of the postextrasystolic beat.

Conclusions

1. The delay in S-A conduction after an interpolated atrial premature systole is in the range of the delay encountered in the analogous disturbances of A-V conduction.

2. The new evidence for the analogy between disturbed A-V and S-A conduction tends to support the view that clinical S-A block is a disturbance localized within the structure of the S-A node. This is substantiated by the fact that the interpolated ectopic atrial beats do not show an aberrant contour, and that the delay in S-A conduction after interpolation occurs without aberrant intra-atrial conduction of the postextrasystolic sinus impulse.

3. The postextrasystolic prolongation of S-A conduction is an effect of concealed A-S conduction, a phenomenon hitherto unreported.

4. The combination of atrial parasystole and interpolation (pseudointerpolation) of atrial premature systoles also represents a hitherto unreported observation.

REFERENCES

1. Kaufmann, R., and Rothberger, C. J.: Ein Fall von ventrikulärer Parasystolie mit einfachen tabellenmässigen Beziehungen zwischen Normal- und Extrarhythmus, Arch. exper. Path. u. Pharmakol. 97:209, 1923.
2. Jervell, A.: Ein Fall von Vorhofparasystolie, Acta med. scandinav. 79:197, 1932.
3. Katz, L. N., Eichelbacher, J. L., and Strauss, S.: An unusual case of ventricular parasystole showing escape [illegible], Am. Heart J. 14:[illegible], 1937.
4. Scherf, D., and Schott, A.: Extrasystoles and allied arrhythmias, New York, 1953, Grune & Stratton, Inc.
5. Velasco Lombardini, R., [illegible], E. J., Ana[illegible], E. D., and Rivero, C. H.: Fisiopatología del ritmo cardíaco, Montevideo, 195[illegible], Fundación Procardias.
6. Scherf, D., Yildiz, M., and De Armas, D.: Atrial parasystole, Am. Heart J. 57:507, 1959.
Fisch, C., and Chevalier, R. B.: Intermittent atrial parasystole, Circulation 22:1229, 1960.
8. Lesser, M. E., et al.: Atrial parasystole (in preparation).
9. Geiger, [illegible], and Georgopulos, G.: Beitrag zur Frage der interpolierten supraventrikulären Extrasystolen beim Erwachsenen, Ztschr. ges. exper. Med. 63:130, 1928.
10. Weinberg, H. B., and Katz, L. N.: T[illegible] unusual types of electrocardiograms, Am. Heart J. 19:519, 1940.
11. Katz, L. N., and Pick, A.: Clinical electrocardiography. Part I. The arrhythmias, Philadelphia, 1956, Lea & Febiger.
12. Spang, K.: Rhythmusstörungen des Herzens, Stuttgart, 195[illegible], Georg Thieme.
13. Pick, A., Langendorf, R., and Katz, L. N.: Depression of cardiac pacemakers by premature impulses, Am. Heart J. 41:49, 1951.
14. Langendorf, R.: Ventricular premature systoles with postponed compensatory pause, Am. Heart J. 46:401, 1953.
15. Katz, L. N., Langendorf, R., and Cole, S. L.: An unusual effect of interpolated ventricular premature systoles, Am. Heart J. 28:16, 1944.
16. Scherf, D., Bornemann, C., and Yildiz, M.: A-V nodal parasystole, Am. Heart J. 60:179, 1960.
1[illegible]. Hoff[illegible], A. N., and Brow[illegible], G. P.: Observations relating to the [illegible] electrical currents of heart muscle, with especial reference to the mammalian auricle, Heart 15:[illegible], 19[illegible].
18. Kaufmann, R., and Rothberger, C. J.: Beitrag zur Kenntnis der Entstehungsweise extrasystolischer Allorhythmien, Ztschr. ges. exper. Med. 5:349, 191[illegible].
19. Langendorf, R., and Pick, A.: Approach to the interpretation of complex arrhythmias, Progr. Cardiovas. Dis. 2:70, 1960.
20. Lewis, T.: The mechanism and graphic registration of the heart beat, London, 1925, Shaw & Sons.

Effect of infusion of saline on response of blood pressure to intravenous tetraethylammonium chloride

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The normal response to the intravenous administration of the ganglionic blocking agent tetraethylammonium chloride (TEAC) is complex. It involves a tachycardia and a transient and small pressor response followed by a marked fall in blood pressure. In patients with acute glomerulonephritis, pheochromocytoma, and in some hypertensive patients with unilateral renal vascular lesions, a marked exclusively pressor response to TEAC has been demonstrated. Pressor responses have also been demonstrated in dogs made hypertensive by renin, angiotensin, or cellophane perinephritis and in nonhypertensive nephrectomized dogs.[3] Both dogs[3] and human subjects[4] receiving infusions of epinephrine and norepinephrine respond to TEAC with a rise in blood pressure.

It has been suggested that the response of blood pressure to ganglionic blockade produced by TEAC might be useful in predicting the response to surgical procedures by patients who are known to have renal vascular lesions in association with hypertension.

Since a pressor response to TEAC has been demonstrated in a variety of clinical and experimental situations, this study was designed to test the effect of another variable, the acute administration of saline, on the response of blood pressure to TEAC.

Materials and methods

Nine hospitalized patients and one house officer were studied. There was no evidence of cardiovascular or renal disease in any patient. The age of the subjects ranged from 13 to 30 years. Most of the patients had been admitted for minor surgical procedures not related to chronic or generalized illness.

Under minimal local skin anesthesia, a 15-gauge needle was introduced into an arm vein, a slow drip of 5 per cent dextrose and water was started, and blood pressure was allowed to stabilize before the test was continued. Control blood pressures were recorded.

Four hundred milligrams of TEAC were then introduced rapidly through the rubber tubing at the site of infusion, and blood pressure was measured with an ordinary

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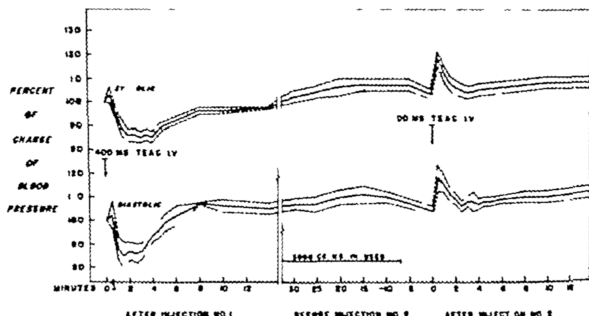


Fig. 1. Effect of infusion of saline on response of blood pressure to TEAC. The solid line represents mean blood pressure responses of 10 subjects plotted as per cent change from control level. The dashed line represents one standard deviation from the mean.

sphygmomanometer at intervals of 30 seconds for 6 minutes and at intervals of 1 to 2 minutes throughout a period of 15 minutes. The response to this injection was considered to be basal for this individual.

After the blood pressure returned to control levels, approximately 3,000 ml. of warmed normal saline was infused within a period of 30 minutes. In the first 2 patients, another 400 mg. of TEAC was given immediately at the end of the infusion. In the last 8 patients, however, a stabilization period of from 5 to 10 minutes elapsed before the second injection of 400 mg. of TEAC was given. The time for stabilization was introduced in order that the period of rapid redistribution of saline across capillary membranes might be completed.

Results

The normal depressor response to TEAC was converted to a pressor response in all subjects by the infusion of normal saline.

Fig. 1 shows a slight initial pressor response followed by an abrupt fall of 15 per cent in systolic and diastolic pressures. A gradual return to the base-line pressures occurred in approximately 15 minutes. This is the expected response in normal individuals. During the infusion of saline there was a slight rise in blood pressure initially, but by the end of the infusion the pressures approached the original base line. Had the first 2 patients been allowed a period of stabilization at the end of the infusion, the mean blood pressure line would have approached the base line even more closely.

The injection of TEAC after the infusion of saline produced a rise of 18 per cent in both systolic and diastolic pressures. The pressor response occurred within the first minute after injection and was not sustained, but no drop in pressure below the base line occurred.

Discussion

In 1948 Brust and associates[4] reported the effects of the administration of TEAC in 2 groups of pregnant women: one group was considered to be normal and the other group was considered to have toxemia of pregnancy. The authors found that in the normal pregnant patient the fall in blood pressure produced by TEAC was considerably greater than that in normal nonpregnant women, i.e., the

"TEAC floor" was lower. In those with toxemia, however, the "TEAC floor" was consistently higher but returned to normal in the postpartum period. They suggested that the hypertension of toxemia was supported by an excessive degree of humoral tone, since neurogenic tone had been blocked with TEAC. They also concluded that in the normal pregnant patient the maintenance of blood pressure was due to increased neurogenic tone since the administration of TEAC produced such a profound drop in blood pressure.

Page and McCubbin[3] demonstrated that the usual depressor effect of TEAC could be reversed in dogs made hypertensive by the administration of renin, angiotensin, epinephrine or norepinephrine. They also showed that a similar reversal occurred in dogs in the malignant phase of hypertension produced by cellophane perinephritis, and in normotensive dogs after nephrectomy. Wilber and Brust[4] later showed that the normal blood-pressure response to TEAC in man was reversed when the subjects were made hypertensive with epinephrine and norepinephrine.

Brust and Ferris[1] studied responses to TEAC in 14 patients who were considered for renal surgery for cure of hypertension. Nephrectomy was performed on 10 patients. Of the 5 patients who had parenchymal renal disease none responded to operation. Four of the 5 patients who had vascular lesions were "cured." The response of the "cured" group to TEAC was strikingly different from that of the "surgical failure" group. All patients who were "cured" exhibited a pressor response to TEAC, whereas the patients in the "surgical failure" group showed a depressor response. They concluded that no fall in blood pressure or a pressor response might be useful in characterizing the hypertension as being caused by a demonstrated renal vascular lesion and might suggest potential reversibility of the process.

In contrast to these abnormal responses to TEAC, which were thought to be a consequence of the etiological or pathogenetic agent which caused the hypertension, several patients have been seen at Grady Memorial Hospital in whom a pressor response became a depressor response within a matter of days after diuresis and other therapy. This suggested that expansion of plasma volume or content of sodium in the body might be other causes of a pressor response.

Frye and Braunwald[6] have recently reported upon the effects which acute hypervolemia has on circulatory dynamics in the presence and absence of ganglionic blockade. They found that an increase in blood pressure and cardiac output were minimized in the presence of an intact autonomic nervous system but that when ganglionic blockade was effected, there was a significant increase in arterial blood pressure and cardiac output with expansion of blood volume. These findings appear to indicate that the normal responses to hypervolemia are mediated throughout the autonomic ganglia and tend to prevent an increase in cardiac output and blood pressure by reflex enlargement of the vascular bed and depression of myocardial contractility. The data presented here are compatible with this concept.

It is apparent that a pressor response to TEAC is not specific for hypertension on the basis of unilateral renal disease, circulating humoral pressor agents, or hypervolemia, but it may occur with any one of them. In many of the situations in which a pressor response has been described (i.e., toxemia, acute glomerulonephritis) retention of water and salt and hypervolemia are present and contributory. One can infer from the available data that a pressor response occurs when the general autonomic activity is blocked at the time at which its net function is to minimize a rise in blood pressure.

Summary and conclusions

1. The response of blood pressure to the intravenous administration of TEAC has been evaluated in 10 normal subjects before and after hypervolemia was induced by the infusion of saline.

2. A reversal in the normal depressor response to TEAC has been produced by the induction of hypervolemia.

3. These data and the data of others suggest that a pressor response to TEAC is not specific for renal hypertension, circulating pressor substances, or hypervolemia.

REFERENCES

1. Brust, A. A., and Ferris, E. B.: The diagnostic approach to hypertension due to unilateral kidney disease, Ann. Int. Med. 4:1019, 1957.
2. La Due, J. S., Murison, P. J., and Pack, G. T.: The use of tetraethylammonium bromide as a diagnostic test for pheochromocytoma, Ann. Int. Med. 29:914, 1948.
3. Page, I. H., and McCubbin, J.: The pattern of vascular reactivity in experimental hypertension of varied origin, Circulation 4:70, 1951.
4. Wilber, J. A., and Brust, A. A.: The circulatory and metabolic effects in man of histamine, Mecholyl, tetraethylammonium, and atropine in the presence of circulating epinephrine and norepinephrine, J. Clin. Invest. 37:476, 1958.
5. Brust, A. A., Assali, N. S., and Ferris, E. B.: Evaluation of neurogenic and humoral factors in blood pressure maintenance in normal and toxemic pregnancy using tetraethylammonium chloride, J. Clin. Invest. 27:717, 1948.
6. Frye, R. L., and Braunwald, E.: Studies on Starling's law of the heart. I. The circulatory response to acute hypervolemia and its modification by ganglionic blockade, J. Clin. Invest. 39:1043, 1960.
7. Acheson, G. H., and Moe, G. K.: The action of tetraethylammonium ion on the mammalian circulation, J. Pharmacol. & Exper. Therap. 87:220, 1946.

Portable blood pressure recorder
Accuracy and preliminary use in evaluating intradaily variations in pressure

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The inherent variability of the blood pressure has led to problems in the diagnosis,[1,2] treatment,[3] and prognosis[4,5] of hypertension. Knowing how the blood pressure fluctuates with the stresses and strains of everyday life should help in assessing the severity of hypertension, the response to treatment, and the prognosis in individual cases.

The portable blood pressure recorder described in this report was developed as a means of obtaining new information on variations in blood pressure throughout the day. The recorder is worn by the subject as he carries out his daily routine, the readings are taken semiautomatically, and the results are recorded on tape. Otherwise, the technique of determining the blood pressure is similar to that of the standard auscultatory method. This similarity allows comparison of determinations by the two methods and the use of established standards in evaluating the results.

This report deals with preliminary observations on measurements of blood pressure with the portable recorder in normotensive subjects. The purpose of the studies was (1) to compare the values obtained with the portable instrument with those obtained with the standard auscultatory method and (2) to measure the variability of blood pressure under everyday living conditions.

Materials and methods

Portable blood pressure recorder. The portable recorder* (for convenience also referred to as *portometer*) is illustrated in Fig. 1. It consists of a standard blood pressure cuff with bulb, a button microphone, a frequency-modulated pressure transducer and appropriate electronic equipment, a tape recorder controlled by a pressure switch, and a twin light signal system.

The recorder is worn by the subject as shown in Fig. 2. The blood pressure cuff is wrapped around the upper arm and secured with adhesive tape. The inflating bulb is placed in the axillary area, and the microphone, which acts as a substitute

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Development of this instrument was made possible by grants from the Mrs. William A. [illegible], [illegible], and Mr. J. W. [illegible]. Research was supported in part by grants from the San Francisco Heart Association, and from the United States Public Health Service (H 734).

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*The recorder used in these studies was assembled by the Alpha Scientific Laboratory, Berkeley, Calif., under the direction of Dr. J. R. [illegible]. An improved model, smaller and lighter in weight, is being developed by the [illegible] Company, San Francisco, Calif.

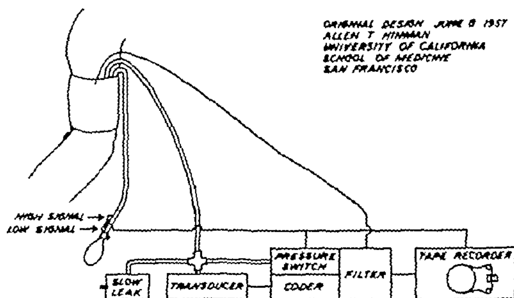


Fig 1 Diagram of portable blood pressure recording system

for the stethoscope is taped over the brachial artery The tape recorder is carried in one shoulder bag and the batteries, transducer and electronic equipment in the other The weight of the present equipment is 5 ½ pounds

Method of recording The pressure switch is set at a level above systolic pressure this setting is not known to the subject In order to minimize noise from clothing the subject is asked to extend the arm and avoid unnecessary movement To start the recording cycle the subject inflates the cuff At a cuff pressure of 50 mm Hg the pressure switch turns on the pressure transducer the tape recorder and the low lamp of the signal system Inflation is continued until lighting of the high lamp signals to the subject that the cuff has been inflated above systolic pressure and that inflation should be stopped The cuff deflates in approximately 30 seconds through an adjustable needle valve As the cuff pressure decreases the air flow aperture increases in size producing a linear drop in cuff pressure During deflation the pressure in the cuff is continuously recorded on the tape through the transducer The pulse sounds (Korotkoff) are picked up by the microphone over the brachial artery and recorded on the tape When the pressure in the cuff reaches 50 mm Hg the pressure switch opens stopping the tape recorder and the transducer It also turns off the low signal lamp the subject can then deflate the cuff completely

When a set of recordings has been completed the tape is decoded through a system calibrated with a mercury manometer The frequency modulated pressure signal is converted into a direct-current potential which is played back through a pen recorder The arterial sounds are converted to deflections on the pen recorder and at the same time are monitored by means of an audiosystem

Experimental observations

Simultaneous bilateral determinations of blood pressure The validity of measurements by the portable recorder was determined in studies on 5 normotensive subjects In each study the subject's blood pressure was determined by using the portable recorder on one arm and the standard auscultatory pressure cuff on the other as shown in Fig 3 Readings by the two methods were taken simultaneously at 2 minute intervals, and the pattern of recording was kept constant The portometer was used for 6 determinations on the left arm was shifted to the right arm for 12 determinations, and was then changed back to the left arm for an additional 6 determinations, while an



Fig 2. Subject wearing portable blood pressure recorder Left shoulder bag contains transducer and electronic equipment, and right shoulder bag contains the tape recorder

equal number of auscultatory readings were taken on the opposite arm. In this manner 24 simultaneous recordings were taken 12 on each arm by each method as shown in the representative study presented in Fig 4. This technique enabled us to detect bilateral inequalities in the subject's blood pressure and to balance the effect of adaptation

Determinations of blood pressure were made as described on 9 occasions. The systolic and diastolic pressures recorded in the left and right arms of the subjects, the average of 12 readings by each method are compared in Fig 5 In the left arm the average systolic pressures measured by the portometer were in almost exact agreement with the auscultatory readings in 3 experiments, were lower in 5 experiments, and higher in 1 With one exception (Subject R. T Experiment 2) the pressures recorded in the left arm by the two methods did not differ by more than 6 mm Hg In the right arm the systolic pressures recorded by the portometer were lower than the auscultatory readings in 7 experiments and higher in 2 Here, the difference between the two readings was 9 mm. Hg or less. Comparison of the levels recorded during the 9 studies showed that the recorder underestimated systolic pressure a total of 5 times in the left arm and 7 times in the right arm. The average error however was negligible. If the one experiment on Subject R T is excluded the underestimation amounted to less than 2 mm Hg in the left arm and less than 4 mm Hg in the right arm

Readings of diastolic pressure by the portable recorder were less satisfactory In general the diastolic pressures appeared to be recorded at a point between the muffling and the disappearance of the sound As shown in Fig 5 the average recorded pressures were intermediate between Phase IV and Phase V in the 9 determinations on the right arm and in 6 of the 9 determinations on the left arm. These differences were in the range of 4 mm. Hg In the other 3 determinations on the left arm the inaccuracy was greater (see Subjects K.C M C and R.T in Fig 5) In these instances the pressures recorded by our instrument were closer to Phase IV than to Phase V

The finding of different pressures in the two arms (Fig 5) although incidental to this study deserves mention Our subjects consistently had higher systolic pressures in the right arm than in the left amounting to as much as 15 mm. Hg in some cases, and with two exceptions (Subjects C T and K.C) the diastolic pressures in the right arm were also higher Similar disparities in the levels of pressure in the

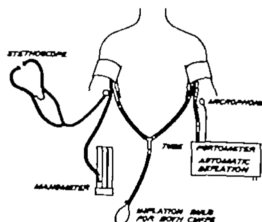


Fig 3 Technique for taking simultaneous readings of blood pressure with portable blood pressure recorder and by standard auscultatory method. Both cuffs are inflated simultaneously by means of bulb and Y tube deflation is regulated by needle al of portable recorder

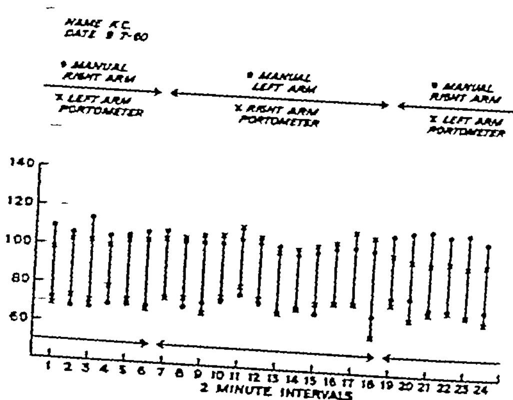


Fig. 4. Results of simultaneous bilateral blood pressure readings in representative study on portometer. Subject K.C. x = Reading taken with the portable blood pressure recorder. • = Reading taken by standard auscultation method.

ght and left arms have been noted in other studies.

In determining the validity of measurements by the portable recorder, we also took simultaneous readings on the same arm with the stethoscope in the usual position. This necessitated placing the microphone over the brachial artery but proximal to the stethoscope, which, in our opinion, introduced another variable. For this reason, we preferred to use the bilateral method.

Use of portable recorder in determining variations in pressure. Additional studies were carried out to evaluate the use of the portable recorder in measuring variations in the level of blood pressure throughout the day. Three subjects, one of whom had levels which were frequently in the higher ranges, wore the portable recorder for various periods while following their usual daily routines. Each recorded his blood pressure at intervals and noted his activity at the time at which each reading was taken.

The subjects were able to wear the portometer for as long as 8 to 11 hours without discomfort, although the present equipment is somewhat heavy and cumbersome. The pressures recorded by each of the 3 subjects and his activity at the time of the reading are indicated in Figs. 6, 7 and 8.

Subject B.T.E. recorded his pressure 24 times in a period of 8 hours. During this time his level of systolic blood pressure ranged from 93 to 140 mm. Hg, averaging 113 mm. Hg (S.D. 12.9), and his diastolic pressure ranged from 71 to 93 mm. Hg, averaging 77 mm. Hg (S.D. 5.9). In a similar study, Subject A.H. recorded 22 readings of blood pressure over a 10-hour period. His systolic pressure ranged from 109 to 170 mm. Hg, averaging 130 mm. Hg (S.D. 6.2), and his diastolic pressure ranged from 63 to 104 mm. Hg, averaging 81 mm. Hg (S.D. 10.6). In the third study, the pressure switch was set at 250 mm. Hg. Because the cuff was uncomfortably tight when inflated

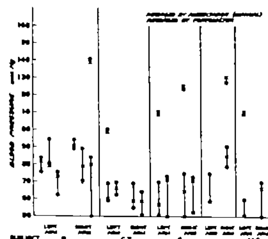


Fig 5 Comparison of blood pressure readings obtained simultaneously by portable recorder and standard auscultatory method in experiments on 5 normotensive subjects. Each line represents the average of 12 readings on one arm.

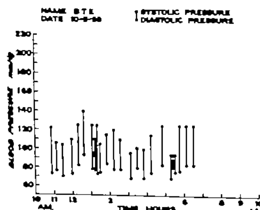


Fig 6 Levels of blood pressure determined with the portable recorder by Subject B.T.E. during the routine of a normal day Activities included reading (11:00 to 12:00 A.M.), technical discussions at work (12:30 to 2:00 P.M.), driving in traffic (5:45 P.M.), and playing with his children (6:30 P.M.).

only 9 determinations during an 11-hour period. The recordings during this time showed that his systolic pressure ranged from 138 to 190 mm Hg averaging 171 mm Hg (S.D 25.9) and that his diastolic pressure varied from 93 to 139 mm Hg averaging 120 mm Hg (S.D 19.8)

Discussion

The portable blood pressure recorder was designed primarily to provide information on intradaily variations in the level of blood pressure in patients with hypertension Our preliminary observations on normotensive subjects indicated that the portable recorder is sufficiently accurate for this purpose. Although the levels of blood pressure established by the portometer and the standard auscultatory method were not in complete agreement, the discrepancies were not serious. The disparity between the systolic pressures recorded by the two methods was slight. The difference between the diastolic pressure readings, although greater in degree

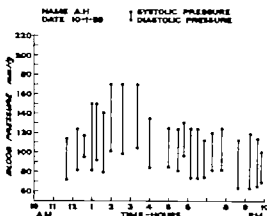


Fig 7 Levels of blood pressure determined with the portable recorder by Subject A.H. over a 10-hour period. Activities included driving in traffic (1:00 P.M.), speaking at a meeting (2:00 to 3:30 P.M.), and resting at home (9:45 P.M.).

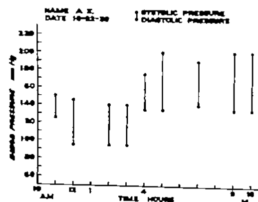


Fig 8 Levels of blood pressure determined with the portable recorder by Subject A.Z. The first 4 determinations were made when the subject was alone and reading quietly the next 2 were made when he was in heated discussion about some phase of his work, and the last 3 were made when he was at home caring for his children.

does not invalidate readings obtained with the portable recorder particularly since the auscultatory method is somewhat unreliable because of differences in keenness of hearing among observers and the difficulty sometimes found in identifying Phases IV and V. In addition our special interest lay in determining changes in pressure over a period of time and in a series of such determinations any constant error would tend to be cancelled.

The differences in blood pressure determinations with the portable recorder were usually in multiples of 4 mm Hg. This is the drop in pressure in the cuff between two heartbeats indicating that the present instrument does not always record the first heartbeat probably because of faulty coupling of the microphone to the skin. Imperfect coupling was also thought to be mainly responsible for the inaccuracy in recording diastolic pressures. The tape recorder may have been partly at fault however since the frequency of pulse waves in the Phase IV to Phase V band is below the lower distortion free limit of our present apparatus (about 100 cycles per second). Technical improvements to minimize errors in recording and to reduce the size and weight of the equipment are currently under way.

Despite some limitations of the present equipment the portable recorder offers a practical technique for measuring the blood pressure. It has the advantage of allowing frequent recordings during the day in contrast to the usual single casual reading by the auscultatory method. Since the subject initiates the recordings the pressor effect which results from the presence of a physician or observer[1] is eliminated. In addition the subject is not aware of the level of his blood pressure.

Preliminary data obtained with the portometer indicate that the blood pressure varies significantly during the course of a day and that these variations can be related to experiences in the everyday life of the subject. In the future comparable studies on hypertensive patients should yield useful information for diagnostic and prognostic purposes as well as for regulating drug therapy.

Summary

The portable blood pressure recorder described in this report offers a practical technique for determining intradaily variations in the level of pressure. The instrument is worn by the subject enabling him to record his blood pressure at frequent intervals during the day while in his usual environment and performing his usual tasks. The readings are taken semiautomatically and the aid of a physician or technician is not required. The subject does not know the levels recorded by the instrument.

Preliminary observations on normotensive subjects showed that the portable recorder is sufficiently accurate for clinical purposes. In additional experiments 3 subjects recorded their levels of pressure at intervals while carrying out their daily routines. The results indicated that the portable recorder provides valid data on variations in blood pressure throughout the day. Expanded studies on hypertensive patients should yield useful information for evaluating the highly variable natural history of hypertension.

REFERENCES

1. Ayman, D. and Goldshine, A. D. Blood pressure determinations by patients with essential hypertension. I. The difference between clinic and home readings before treatment. Am. J. M. Sc. 200:465, 1940.
2. Smirk, F. H. High arterial pressure. Springfield, Ill., 1957, Charles C Thomas, Publisher.
3. Freis, F. D. The discrepancy between home and office recordings of blood pressure in patients under treatment with pentapyrrolidinium. Importance of home recordings in adjusting dosages. M. Ann. District of Columbia 23:363, 1954.
4. Janeway, T. C. A clinical study of hypertensive cardiovascular disease. Arch. Int. Med. 12:755, 1913.
5. Blood Pressure Study 1939. The Actuarial Society of America and the Association of Life Insurance Medical Directors, New York, 1940.
6. Sokolow, M. and Perloff, D. The prognosis of essential hypertension treated conservatively. Circulation 23:697, 1961.
7. Amsterdam, B. and Amsterdam, A. L. Disparity in blood pressures in both arms in normals and hypertensives and its clinical significance: a study of 1,000 normals and 272 hypertensives. New York J. M. 43:2294, 1943.

Diastolic balloon pumping (with carbon dioxide) in the aorta—A mechanical assistance to the failing circulation

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Mechanical assistance to the failing heart has been tried in a number of experiments.[1-7] Arterioarterial or venoarterial pumping was so timed by means of electronic devices that the ejection of blood into the vascular system could occur during the diastolic phase of the cardiac cycle. The purpose of diastolic pumping devices is to increase the flow of blood during diastole, especially through the coronary arteries, to decrease the end-diastolic pressure, and therefore to decrease the work of a failing left ventricle.

This report discusses experiments on dogs with a simple device that allows diastolic pumping without taking the blood outside the body.

Materials and method

A latex tubing* was tied around the end of a polyethylene catheter† with multiple side holes. The distal end of the polyethylene catheter was occluded so that the tubing could be inflated and deflated through the side holes in the catheter (Fig. 1).

A polyvinyl catheter balloon for use on human beings has recently been made available commercially.‡ The proximal (uncovered) end of the catheter was connected to an elastic Tygon tube with thick walls. This tube fits in an aluminum rigid wall cylinder with two stoppers. The tubing, the catheter, and the balloon formed a closed system that was filled with carbon dioxide through a three-way stopcock attached to the aluminum cylinder.

Air pressure was applied intermittently to the tube in the cylinder, and the carbon dioxide was expelled to inflate the balloon. The pressure was regulated by means of a three-way solenoid valve.§ The dead space in the system was diminished by filling the cylinder surrounding the tube with sterile saline solution.

The solenoid valve was activated from the R wave of the electrocardiogram through a timing device that amplifies

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*Diameter 0.95 cm., length 30 cm. Penrose latex drainage tubing, U.S. Alox Company, St. Louis, Mo.

†External diameter 2.23 mm., internal diameter 1.16 mm., length 60 cm. Polyethylene tubing, Intramedica, Clay Adams, Inc., New York, N. Y.

‡[illegible] Catheter Instruments Company, Glens Falls, N. Y.

§Skinner Electric Valve Division, Solenoid Valve Company, New Britain, Conn. Valve [illegible] inlet diameter 1/8 inch, outlet diameter 3/32 inch.

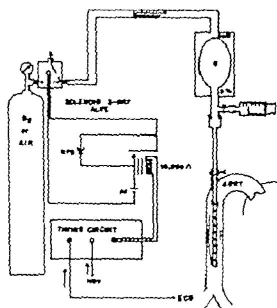


Fig. 1. Diagram of the entire setup, including the intra-aortic tube, the outside balloon, the air pressure system, and the electronic devices for the timing of the inflation. *NaCl* indicates the sterile 0.9 per cent solution of sodium chloride around the outside balloon to decrease the dead space in the system. The amount of carbon dioxide can be regulated with the syringe.

the R wave voltage and activates the valve with an impulse of variable but pre-fixed duration and variable but predetermined delay. A Cardiac Programmer* was used.[3]

The entire system could be sterilized with ethylene oxide.

Tests conducted in a mock circulation (*Fig. 2*). The balloon-carrying catheter was inserted into the mock aorta Tygon tube (internal diameter 1.9 cm.) in which a diastolic pressure of 125 cm. of water was maintained. The inlet pressure was 20 cm. of water and there was only one tricuspid polyurethane valve[4] in the system placed at the inlet. A flowmeter was used in the circuit so that the flow per minute could be read directly. Pressure tracings were obtained with Statham gauges from the catheter system and the Tygon tube. All testing was done with water of 37°C. instead of blood.

Several types of catheters were tested initially as to the number and location of the air inlet holes and the number of constrictions of the latex tubing. We found that the number of holes was immaterial above a certain limit, and that the best flow was obtained when there was constriction at no point of the latex tubing.

The whole system was tested as to the following variables in relation to flow: air pressure in the rigid-wall cylinder, carbon dioxide in the catheter-balloon system, length of the latex tubing, length of the stroke, and diameter of the Tygon aorta. We found that the maximal blood flow (1,600 ml. per minute) was obtained under the following conditions (Fig. 3): air pressure of 1,961 grams per square centimeter (27 p.s.i.), volume of 25 ml. carbon dioxide, 20 cm. length of latex tubing, stroke duration of 120 milliseconds, and diameter of the Tygon aorta at least twice the diameter of the latex tube.

The optimal duration of the stroke varied with the air pressure and the amount of carbon dioxide in the system, as well as with the rate of pumping. The amount of carbon dioxide in the system may be varied with a syringe, and an optimum can be found. Low pumping rates (e.g., 60 strokes per minute) permit long stroke duration (e.g., 150 msec.), whereas with high pumping rates (e.g., 112 strokes per minute) the stroke had to be short (e.g., 70 msec.). Sufficient time had to be allowed for evacuation of the carbon dioxide from the latex tubing.

During this testing we also found that

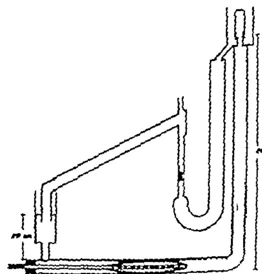


Fig. 2. Diagram of the mock circulation system used to test the intra-aortic pump.

*Cardio Corporation, Miami, Fla.

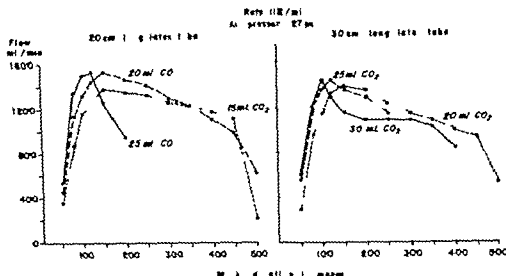


Fig. 3. Curves showing the changes in flow in the mock circulation after the changes in duration of the stroke. Various curves are obtained by varying the amount of carbon dioxide in the system and the length of latex tubing. The highest flow is obtained by a tube 20 cm. long which contains from 20 to 25 ml. of carbon dioxide.

the inflation and deflation of the latex tube could be rapid and complete if the amount of gas leaving the outlets of the solenoid valves was reduced. For this purpose the space in the rigid-wall cylinder was decreased by filling it with a 0.9 per cent solution of sodium chloride in water. In that way the pressure curves generated in the blood by the inflation of the latex tube became narrowed and their length came close to the stroke length set on the timing device (from 20 to 40 msec. longer). For example, if the stroke length of the Programmer was set at 120 msec., the acutal resulting pressure curve would be from 20 to 40 msec. longer, i.e., from 140 to 160 msec.

Testing in dead dogs. By pumping the latex tubing into the aorta of dead dogs, we were able to create a pulsating flow with a pressure of 80/60 mm. Hg but only when an initial pressure of 40 mm. Hg had been created first in the arterial system by rapid infusion of a 0.9 per cent solution of sodium chloride in water.

Testing in live anesthetized dogs. A 20 cm. length of latex tube was inserted into the thoracic and abdominal aorta through the left carotid or subclavian artery. Mongrel dogs which had a body weight of 15 to 20 kilograms were anesthetized with Nembutal sodium. Pressures were recorded by means of Statham gauges (P23Db, 12V, 0-75 cm. of Hg) from the left femoral artery, the right brachial artery, the left ventricle, and the left atrium. The left ventricle and the left atrium were catheterized through the left auricular appendix after left thoracotomy. The signal of the timing circuit was recorded so that the exact location and length of the pump stroke are also indicated in the tracing. The blood flow was recorded by means of an electromagnetic flowmeter* at the left femoral artery and the brachiocephalic trunk.

The time of delay from the R wave of the electrocardiogram was regulated according to the heart rate. We found that it was practical to calculate the optimal delay by the formula: D = RR − (S+40), where RR is the length of one cardiac cycle in milliseconds, and S is the stroke time in milliseconds. For example, when the cardiac cycle (RR) was 400 msec. (150 beats per minute) and the stroke was 120 msec., the delay was set at 400 − (120 + 40) = 240 msec. Improper delay time caused the pump stroke to operate during systole and to be superimposed on the heart pressure wave. As a result of this mistiming, the load imposed on the

*Medcraft, PM-4, Medcraft Division, Quality Precision Products, Inc., Los Angeles, Calif.

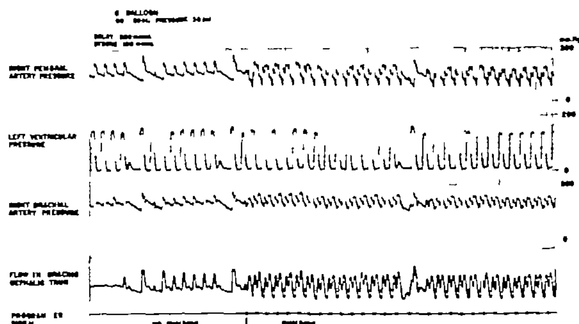


Fig. 4. Graphs of blood pressures and flow before and during intra-aortic balloon pumping. The pump pressure wave in diastole is higher than the heart wave in both the femoral and the brachial arteries. The left ventricular pressure goes slowly down during the pumping. The end-diastolic pressure in the arteries is lower during pumping. The blood flow in the brachiocephalic trunk due to inflation of the balloon during diastole gives a higher wave than the one caused by contraction of the heart.

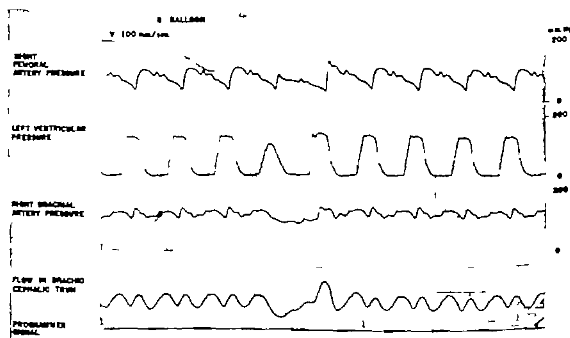


Fig. 5. Record made at high-speed during pumping. The end-diastolic pressure is low in the femoral artery. The flow through the brachiocephalic trunk is considerably increased during diastole.

ventricle was increased Thereafter the pump stroke was not initiated before the dicrotic notch appeared on the aortic pressure tracing which indicated closure of the aortic valve The entire pump stroke had to be completed at least 20 msec before the next ventricular systole began in order to assure lowering of the end diastolic pressure in the aorta (Fig 4) only under these circumstances was the left ventricular pressure reduced

The pressure waves corresponding to the pumping recorded in the brachial and femoral arteries, were higher than those of the heartbeat (Fig 4) The end-diastolic pressure in the arterial system was lowered. The flow through the brachiocephalic trunk was slightly increased and the flow wave due to the pumping was larger than the one due to the heart action (Fig 5) The systolic pressure in the femoral artery was sometimes reduced during pumping possibly because the deflated latex tubing presented an obstacle to the systolic flow in the aorta. However the mean pressure did not change and the flow curves demonstrated that the total flow through the femoral artery was not reduced

When the ventricles were fibrillating the intra aortic pumping did not produce a significant increase in pressures but if the arterial pressure was slightly elevated by cardiac massage the effect of pumping was notable on the pressure tracings (Fig 6)

Cineangiography in human cadaver Finally the balloon was inserted into the ascending aorta of a cadaver half an hour after death Radiopaque dye was injected by means of a common catheter into the ascending aorta. Cineangiographic film taken during pumping showed considerable movement of the dye toward the

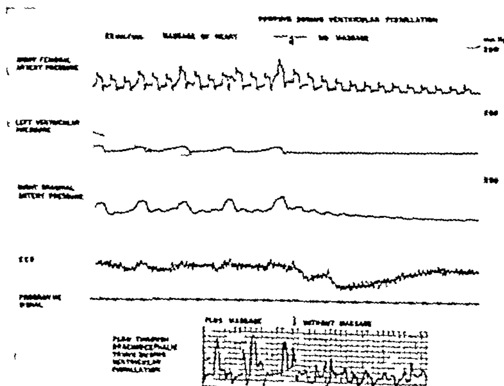


Fig 6 Intra-aortic pumping during ventricular fibrillation. Significant pump waves are recorded only when a pressure of at least 40 mm. Hg is maintained by manual heart massage. Although the left ventricular pressure during manual massage does not rise above 30 mm. Hg, the pressures in the femoral and brachial arteries rise to about 100 mm. Hg. The flow in the brachiocephalic trunk during balloon pumping is also higher during massage

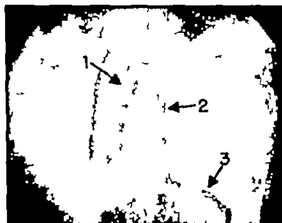


Fig 7 An intra-aortic balloon in the ascending aorta of a human being *1* The middle of the spindle-shaped gas-filled space occupied by the inflated balloon. *2* A common catheter for injections. While the balloon is inflated, the radiopaque dye fills the *coronary artery (3)*. *The heart is in arrest. (Made in* the Cardiovascular Laboratory of Dr Sones.)

coronary (Fig 7) and other peripheral arteries, although the heart was in complete arrest.

Comment

The mechanical device described was designed to assist the heart in maintaining the circulation and to increase the coronary blood flow during diastole. Tests on anesthetized dogs in which we assumed that the circulation was normal showed that intra aortic pumping with the balloon increased the flow of blood in the arterial system during diastole and lowered the end-diastolic arterial pressure. It is obvious that under these conditions the contracting left ventricle has less resistance to overcome in the arterial system Thus, a part of the work of the heart is taken over by the mechanical pump.

The effect of intra-aortic pumping on a failing heart is not known It is difficult to induce left ventricular failure in the dog without causing its death There are indications however that intra-aortic pumping may be of help by relieving the left ventricle of some of its work and by increasing the blood flow and possibly the coronary blood flow during diastole. Failure of the right side of the heart cannot be helped directly by intra-aortic pumping Furthermore intra-aortic pumping is not effective in ventricular fibrillation or in instances of very low arterial pressure in that case the combination of pumping and heart massage increased pressure and flow

The danger of rupture of the intra-aortic latex tube and of gas embolism in the patient is minimal since even though the tube is filled it is not distended during pumping The pressure is not applied directly on the latex tube but on the thick walled balloon outside the body a safety device is provided Moreover the closed latex tube system is filled with carbon dioxide, which would be relatively harmless in case of a leak

The diastolic arterial support to the circulation as described would probably be contraindicated in cases of aortic insufficiency

The advantages of pumping by means of an intra-aortic balloon are these (1) No blood is handled outside the body (2) Only one vessel is cannulated (3) No blood is needed for priming the device (4) The device is very simple

Summary

A device to provide mechanical assistance to the failing circulation is described It consists of a catheter in a long narrow latex tube that was inserted into the descending aorta of an anesthetized dog The latex tube was rhythmically inflated with carbon dioxide through a pressure system and the stroke was triggered with the aid of a timing circuit from the electrocardiogram of the animal The stroke length and the delay after the R wave of the electrocardiogram were preset so that the latex tubing was inflated during diastole and remained deflated during systole

It was possible to increase the diastolic blood flow in the arterial system and lower the end-diastolic arterial pressure It is hoped that the use of this device in the failing heart will result in increased diastolic blood flow improved coronary perfusion and decreased work for the failing left ventricle. The best indication for its use would be a failing left ventricle due to an acute coronary thrombosis.

REFERENCES

1 Clauss, R H Birtwell W C., Albertal, G Lunzer S., Taylor W J Fosberg, A. M nd

Harken, D. E.: Assisted circulation. I. The arterial counterpulsator, J. Thoracic & Cardiovas. Surg. 41:447, 1961.

2. Connolly, J. E., Bacaner, M. B., Bruns, D. L., Lowenstein, J. M., and Storli, E.: Mechanical support of the circulation in acute heart failure, Surgery 44:255, 1958.
3. Salisbury, P. F.: Cross, C. E., Rieben, P. A., and Lewis, R. J.: Comparison of two types of mechanical assistance in experimental heart failure, Circulation Res. 8:431, 1960.
4. Stuckey, J. H., Newman, M. M., Dennis, C., Berg, E. H., Goldman, S. E., Fries, C. C., Karlson, K. A., Blumenfeld, M., Weitzner, S. W., Binder, L. S., and Winston, A.: The use of the heart lung machine in selected cases of acute myocardial infarction, S. Forum 8:342, 1957.
5. Watkins, D. H., and Duchesne, E. R.: Post-systolic myocardial augmentation. Part 1. Developmental considerations and techniques, A.M.A. Arch. Surg. 82:839, 1961.
6. Willman, V. L., Cooper, T., Riberi, A., and Hanlon, C. R.: Cardiac assistance by diastolic augmentation: hemodynamic evaluation in dogs with complete heart block, Tr. Am. Soc. Artificial Internal Organs 7:198, 1961.
7. Jacobey, J. A., Taylor, W. J., Smith, G. T., Gorlin, R., and Harken, D. E.: A new therapeutic approach to acute coronary occlusion, S. Forum 12:225, 1961.
8. Murphy, W. P., Jr.: The Cardiac Programmer to trigger an arterial pump, Tr. Am. Soc. Artificial Internal Organs 7:361, 1961.
9. Akutsu, T., Dreyer, B., and Kolff, W. J.: Polyurethane artificial heart valves in animals, J. Appl. Physiol. 14:1045, 1959.

Mechanisms in the production of atrial fibrillation during asphyxia

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Syracuse N Y

Clinical observations have shown that conditions which tend to produce either localized cardiac or generalized hypoxia predispose the heart to atrial fibrillation [1-3] Thus atrial fibrillation occurs during congestive heart failure coronary artery disease and mitral stenosis. It has been shown[4,5] that asphyxia predisposes the dog heart to atrial fibrillation. Asphyxia or hypoxia produces a complex chain of events which involve both local and reflex changes in the organism [6-9] Characteristic changes include (1) variations in arterial venous and intracardiac blood pressures (2) reflex vagal activity (3) anoxemia (4) hypercapnea (5) sympathetic discharge (6) distention of the walls of the cardiac chambers and (7) decrease in blood pH It is difficult to predict which of these many changes is involved in predisposing the heart to atrial fibrillation This study attempts to elucidate the mechanism of action and to determine the relative importance of some of the factors which influence the production of this arrhythmia

Material and methods

Mongrel dogs of both sexes, which weighed between 14 and 33 kilograms, were anesthetized at first with thiopental (20 to 25 mg Kg) intravenously followed by morphine sulfate (3 mg Kg) intramuscularly and chloralose (50 to 80 mg / Kg) intravenously Femoral arterial and central venous blood pressures were recorded by Statham pressure transducers.

The contents of the thorax were exposed by a mid-sternal incision the pericardium was opened and the heart was cradled in such a way as to expose a large area of the right atrium and its appendage. Artificial respiration was given through an endotracheal tube by means of a Palmer respiration pump Atrial and ventricular electrograms were recorded by means of bipolar metal-clip electrodes, and in most experiments a Lead II electrocardiogram was also taken The recording device used was a Grass multichannel ink writing oscillograph

Three methods for the production of atrial flutter were utilized The method of Rosenblueth and Garcia Ramos[10] was used to induce a circus type of atrial flutter Atrial tissue between the superior and inferior venae cavae was crushed to create an island of nonconducting tissue surrounded by a ring of excitable tissue which allowed the maintenance of a circus type of conduction The second procedure in

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volved the subepicardial injection of 0.05 to 0.1 ml. of a 0.05 per cent aconitine solution which produced a rapidly discharging ectopic focus (Scherf[11]). The third method was the direct electrical stimulation of the atria at flutter rates (350 to 480 impulses per minute). The results obtained appeared to be independent of the type of flutter employed in these studies.

Asphyxia was produced by stopping the respiration pump and clamping the rubber tubing which connected the pump to the endotracheal tube. Degrees of anoxia were induced by allowing the animals to breathe various concentrations of oxygen-nitrogen mixtures. The mixtures were prepared in a large spirometer which was attached to the respiration pump. The percentages of the gaseous components of the mixtures used were measured with a Fry gas analyzer.[12]

Heart-lung preparations were set up by the method of Patterson and Starling[13] as modified by Krayer and Mendez.[14] Right atrial pressure was measured by means of a water or bromoform manometer. Systemic arterial pressure was recorded by means of a mercury manometer connected to a side branch of the arterial cannula. Systemic cardiac output was measured with a Stolnikov Stromuhr. The Starling type of artificial resistance was set at 70 or 80 mm. of mercury. The temperature of the blood was maintained at 37 to 38°C. The initial blood volume of the system was approximately 600 to 700 ml.

Studies on isolated rabbit left atria were performed by suspending the atria in a 50-ml. bath which contained oxygenated Tyrode's solution at 37.5°C. The atria were driven electrically by a Grass stimulator which was set up to trigger a second stimulator so that an extra stimulus could be thrown into the muscle at a known time interval after the driving stimulus. The mechanical responses were recorded by means of a strain gauge on a Grass multichannel polygraph. The strain gauges could be raised or lowered by a rack and pinion, thus stretching or relaxing the muscle preparations. Postextrasystolic potentiation was used as an indicator of the effectiveness of a stimulus.[14]

Results

Asphyxia and hypoxia result in a complex chain of events which affect the heart. The sequence of events observed in 2 dogs subjected to asphyxia while their hearts were beating at a regular sinus rhythm was the following. After an initial increase in systolic and diastolic arterial blood pressures, a progressive fall in blood pressure and rate proportional to the duration of

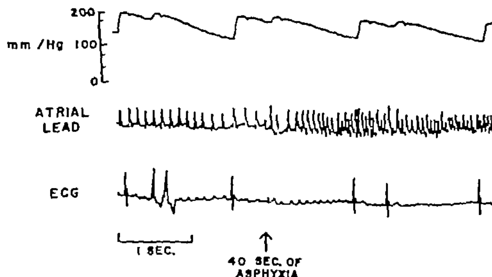


Fig. 1. The conversion of atrial flutter to fibrillation during asphyxia. Female dog, 19 kilograms. Flutter of the circus type. Tracings from top to bottom are: blood pressure, atrial lead, and electrocardiogram (Lead II).

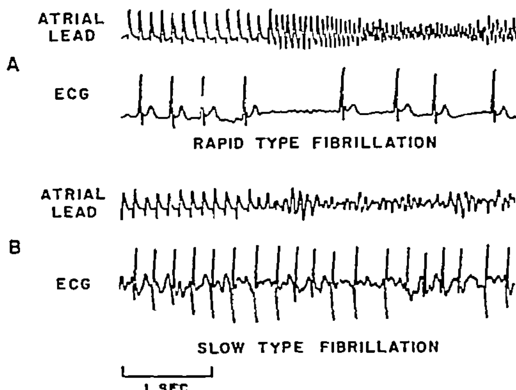


Fig. 2. Types of atrial fibrillation seen in dog atria during asphyxia. A, Fast type. Male dog, 27.5 kilograms, in circus flutter. B, Slow or coarse type. Male dog, 27 kilograms, in circus flutter.

asphyxia occurred, with a return to control values after respiration was resumed. In the late stages of asphyxia the cardiac chambers were visibly enlarged although the central venous pressure was only slightly elevated (3 to 5 cm. of water). In these dogs we did not observe atrial fibrillation. On the other hand, if the atria were beating at flutter rates, asphyxia produced a conversion to atrial fibrillation (see Fig. 1). The atrial flutter rates, although relatively constant in each animal, varied between 350 and 540 beats per minute from animal to animal and usually showed a 2:1 atrioventricular ratio. Between 41 and 150 seconds after the onset of asphyxia the flutter was abruptly converted to fibrillation (average of 102 seconds). The atria fibrillated at rates between 900 and 2,100 beats per minute, with a concomitant irregular ventricular rhythm and rate. These results were observed in 19 out of 22 asphyxia experiments in 13 dogs. In the 3 experiments in which episodes of fibrillation did not occur the flutter rate decreased and was abruptly converted to a regular sinus rhythm. Once atrial fibrillation was obtained, it rapidly reached a maximal rate. If asphyxia was continued, the rate of fibrillation would decrease. Reinstitution of air-breathing resulted first in a temporary increase in the fibrillatory rate, which was then followed by a rapid reversion to the control flutter rate. In those experiments in which a circus type of flutter was used, rebreathing would convert the fibrillation to flutter or to a regular sinus rhythm. No predictions could be made in regard to the type of reversion; furthermore, this could not be related to the initial flutter rate, duration of asphyxia, or the individual animals used. Ventricular rate declined during asphyxia and reverted to control values after the reintroduction of air or oxygen.

The first attempt to analyze the phenomenon of conversion to atrial flutter to fibrillation by asphyxia was an effort to determine the relative importance of hypoxia to hypercapnea. Animals in flutter were artifically respired with oxygen-nitrogen mixtures. In 23 dogs, 58 such procedures were conducted, and atrial flutter was converted to fibrillation in 54

of these. In the rest of the procedures, observed in animals in circus flutter the hypoxia resulted in a decline of the flutter rate and a reversion to a regular sinus rhythm A reduction of inspired oxygen concentration below 10 per cent was required to produce fibrillation The oxygen tension in general, determined the time it took to convert flutter to fibrillation. Thus when 4.3 to 6.3 per cent oxygen was used an average of 122 seconds (in 16 procedures) were required to effect this conversion. On the other hand an average of 80 seconds were required (in 16 procedures) to produce this same conversion when pure nitrogen was used However in view of the wide variations observed in these experiments, it could be assumed that factors other than simple reduction of blood oxygen tension were operative in this phenomenon

If the animals were allowed to breathe mixtures of carbon dioxide (8 to 18 per cent) and air or oxygen no conversion of flutter to fibrillation was observed even after 6 minutes of exposure to these high concentrations. It is likely therefore that the hypoxia rather than the hypercapnea is the important factor in this phenomenon However the possibility that hypercapnea may contribute to the intensity of the phenomenon cannot be excluded

During the course of these experiments the observation was made that in some dogs the fibrillatory rate was high (1,200 to 2 400 beats per minute) whereas in others it was relatively low (600 to 900 beats per minute) (see Fig 2) The animals with high fibrillatory rates usually showed marked slowing of the ventricles, whereas those which displayed the slower type of fibrillation showed only minor changes in the ventricular rate. This suggested that vagal effects were operative in the production of the fast type of fibrillation. It was observed that the ventricular slowing that accompanied the fast type of fibrillation usually was initiated between 5 and 20 seconds prior to the onset of the atrial fibrillation. In an attempt to prove that these effects were indeed vagally induced two types of experiments were performed. The first, conducted on 16 dogs consisted of cutting the vagi or administering atropine sulfate (1 to 2 mg./Kg intravenously) during atrial fibrillation induced

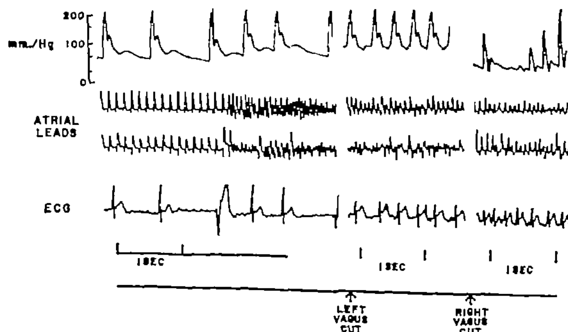


Fig 3 Cutting of the vagi during the hypoxic episode after the initiation of trial fibrillation. *From top downward.* The effects are seen on the arterial blood pressure, atrial activity electrocardiogram (Lead II). Male dog, 27.5 kilograms, in circus type of f——

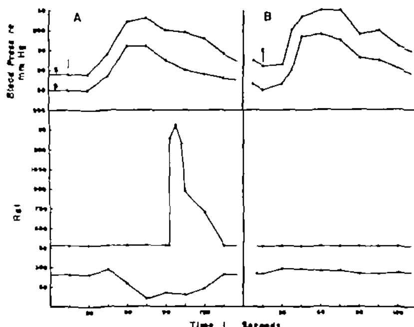


Fig. 4. Effects of the administration of epinephrine to animals in atrial flutter. *A*, Intact preparation. *B*, Atropinized (0.8 mg./Kg.) preparation. *E*, Epinephrine, 8.3 mg./Kg. intravenously. *S*, Systolic pressure. *D*, Diastolic pressure. *A*, Atrial rate. *V*, Ventricular rate. Female dog 24 kilograms, with atria driven electrically at flutter rates.

by hypoxia. If the fibrillation was of the fast type, vagotomy or the administration of atropine sulfate caused a prompt conversion to the slow type of fibrillation with a concomitant rapid rise in ventricular rate (see Fig. 3). In those animals which initially showed the slow type of fibrillation, atropine or vagal cutting had no significant effects on either atrial fibrillation or ventricular rate. In the second type of procedure the same animals which had been vagotomized or atropinized were again subjected to hypoxia. In 23 of 25 procedures a conversion from flutter to fibrillation occurred, but in each of these the fibrillation was of the slow variety (average rate of 773 beats per minute in 16 procedures). In 2 animals which were in circus flutter, the flutter converted to a regular sinus rhythm. Three animals were atropinized and then the vagi were cut. During subsequent hypoxia the results were the same as with atropine alone. These experiments show that in the dog, vagal activity, although not essential for the conversion of flutter to fibrillation by hypoxia, is an important factor in determining the rate and type of atrial fibrillation.

Vagal activity could be initiated via a reflex activation of the carotid-aortic arch area; this resulted from the increase in blood pressure seen in asphyxia or hypoxia. If the vagi were cut, hypoxia caused a fall rather than a rise in blood pressure. On the other hand, the administration of atropine (1 to 5 mg./Kg.) did not eliminate the rise in blood pressure which was due to hypoxia. The question whether the rise in blood pressure which occurs during asphyxia was an important factor which affected the role of reflex vagal stimulation in the conversion of flutter to fibrillation had to be determined. This was studied in two ways. To see whether a rise in blood pressure alone could effect the conversion, epinephrine (5 to 10 μg/Kg. intravenously) was administered to 3 dogs with flutter in 6 procedures. With the subsequent rapid rise in arterial blood pressure a conversion to a fast type of fibrillation promptly occurred, which was accompanied by a marked ventricular slowing (see Fig. 4). In all 3 animals this effect did not occur after either vagotomy or the administration of atropine (2 mg./Kg.). We concluded that the conversion from flutter to

fibrillation by epinephrine was due to reflex vagal stimulation and the results confirm previous work.[18] A second set of experiments was performed in which the rise in blood pressure during hypoxia was prevented by the prior use of adrenergic blocking agents. Dibenamine (8 to 45 mg./Kg.) was administered to 7 dogs. This agent eliminated the rise in blood pressure due to hypoxia, but did not eliminate the vagal factor in the conversion of flutter to fibrillation. A quantitative study however did indicate that this drug reduced the maximum increase in fibrillatory rate produced by asphyxia. Another experimental adrenergic blocking agent SY 28* (1 to 4 mg./Kg.) was used in a similar manner in 2 animals. Hypoxia produced a slight rise in systolic pressure and no rise in diastolic pressure and conversion to a rapid type of fibrillation was seen. Although the atrial rates obtained during fibrillation were higher than those found with Dibenamine they still did not reach the values observed in control hypoxia experiments conducted in the same animals (see Table I). Thus, it is likely that, besides the vagal activation induced by blood pressure hypoxia produces vagal activation by some other mechanism. Stimulation of other reflex areas located in the head and neck or intracranial vagal centers was considered. Attempts were made to produce localized asphyxia in the head. This was done by tying off the left subclavian artery early in the experiment and then when asphyxia in the head was desired clamping off the brachiocephalic artery. This procedure gave variable results. In those dogs in which this phenomenon produced overt signs of asphyxia in the head (gasping type of head movements and cyanosis of the tongue and mucous membranes) conversion of the flutter to a fast fibrillation was observed whereas in those animals in which this procedure failed to elicit these signs no conversion was seen. It is reasonable to suggest that in the latter animals enough blood was supplied to the head via the spinal and or other collateral arteries to prevent the signs of brain asphyxia. We concluded therefore that both the rise in blood pressure and the direct effects of hypoxia of the head and neck were operative in producing the vagal discharge responsible for the conversion of flutter to fibrillation. This does not exclude the possibility of other sources of reflex vagal activation as enumerated by Aviado.[18] He pointed out that reflex vagal activity can be initiated in response to (a) increased intracardiac pressure (chiefly in the right atrium and left ventricle) (b) increased pressure in the pulmonary artery conus, and (c) distention of the chambers of the heart by a balloon or blood.

The role of the intense sympathetic discharge that occurs during asphyxia and hypoxia was studied in two types of experiments. The reflex vagal stimulation which accompanies increased sympathetic activity has been mentioned above. The possibility of direct effects of epinephrine on the atria had to be considered. Atropinized animals were subjected to hypoxia, and their rates of fibrillation were de-

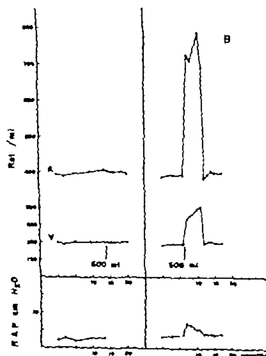


Fig. 5. The effect of a rapid intravenous infusion of saline into an animal in atrial flutter. A, Early in the experiment. B, 250 minutes after the end of A (at this time the heart was dilated and showed signs of failure). 500 ml. Rapid infusion of saline. A, Atrial rate. V, Ventricular rate. R.A.P., Right atrial pressure. 31 lb. dog, 17.3 kilograms, in circus type of flutter.

*SY-28 [illegible]

*Table I. Effect of adrenergic blocking agent SY 28 (N [2 bromethyl] N ethyl 1 naphthalene methylamine) on the atrial fibrillation rate produced by anoxia**

	Atrial rate	*Ventricular rate*	*Arterial blood pressure (mm. Hg)*
Control	440	260	70/0
During anoxia	2 040 (F)	60	210/40
Control after 1 mg./Kg. of SY 28	440	240	70/0
During anoxia	1 620 (F)	55	115/0
Control after total of 2 mg./Kg. of SY 28	440	210	40/0
During anoxia	1 180 (F)	10	110/0

*The fibrillation rate as recorded was the maximum observed during episode of anoxia. Female dog, 17 kilograms. Atria driven at flutter rates by electrical stimulation. F = Flutter.

termined. After recovery, a constant infusion of epinephrine 4 to 5 μg per minute per kilogram was administered with an infusion pump via the femoral vein. The animals were then subjected to hypoxia a second time. There appeared to be no significant difference over the controls. In the same animals 100 to 200 γ of epinephrine was administered either by intravenous or by intracardiac injection at the onset of atrial fibrillation during hypoxia. In each of 3 such experiments there appeared to be no effect on the atrial fibrillation. It is unlikely, therefore, that the direct effects of epinephrine on atrial tissue play a major role in the conversion of flutter to fibrillation during hypoxia.

That fibrillation can still be induced in the denervated atria during hypoxia has been clearly shown. The fibrillation produced by hypoxia in animals which were vagotomized or atropinized is relatively slow and occurs at a time when the hypoxia produced considerable dilatation of the atria. This observation and the work of others[17,19] suggested that dilatation may play a role in predisposing the atria to fibrillation. Two small sutures were attached to the atrial wall and the distance between these markers was measured. In 18 procedures in 8 dogs the distance between markers had increased by an average of 49 per cent (range of 27 to 86 per cent) at the time that fibrillation started during hypoxia. Measurements of right atrial pressure during these experiments indicated only a slight rise which varied between 2 and 5 cm. of water at the time atrial fibrillation had been induced by hypoxia. In another series of experiments a large balloon made of thin rubber was introduced into the right atrial cavity via an opening in the right atrial appendage. The balloon was attached to a 50-ml. syringe. A water manometer was included in the system, thus the balloon could be gradually distended under known pressures. Atrial fibrillation in vagotomized or atropinized preparations could be produced only with an average pressure increase of 24 cm. of water. Only the coarse type of fibrillation was seen. On the other hand, if hypoxia was developing, then distention of the balloon with only 3 to 7 cm. of water pressure would produce the same type of fibrillation. The possibility that the inflated balloon interfered with blood flow and thus manifested its effects by producing hypoxia in the atrial muscle was studied by monitoring the intra-aortic pressure. Indeed, in some instances a decrease in pressure could be demonstrated. However, this was the exception and not the rule. The possibility that the supply of blood to the atrial muscle was impaired by inflation of the balloon was studied with a second set of experiments. The two external jugular veins were cannulated with large cannulae and connected to a large bottle which contained warm saline. Attempts were made to produce distention of the atria by means of rapid infusions of 300 to 500 ml. of saline. Utilization of this procedure in 5 dogs resulted in neither marked atrial distention nor a conversion of atrial flutter to fibrillation; however, when a similar procedure was repeated in 3 of these animals, 3 to 6 hours later, the

same amount of saline produced a marked distention of the atria and a concomitant conversion of atrial flutter to fibrillation which persisted from 1 to 9 minutes (see Fig 5) The success of this procedure during the latter stages of this experiment may be related to the gradual deterioration of the heart action which is observed in these acute experiments. The results obtained were similar to those observed in vagotomized and atropinized animals and in all instances the rate of fibrillation was of the slow variety not exceeding 800 beats per minute.

In 3 heart lung preparations a circus type of flutter was instituted An increase in inflow pressure of 10 to 15 cm. of water over control values was produced by raising the venous reservoir over a period of 10 to 15 seconds. Conversion of flutter to fibrillation was seen in 2 of the 3 preparations, but only after the rise in inflow pressure produced a marked dilatation of the atria and an increase in right atrial pressure of from 8 to 17 cm. of water In the other heart-lung preparation the rise in inflow pressure did not induce a conversion of flutter to fibrillation. However after heart failure was produced by the injection of 90 mg of pentobarbital per liter of blood an increase in inflow pressure of only 5 to 10 cm. of water promptly produced atrial fibrillation with a concomitant rise in right atrial pressure (see Fig 6) It is clear that an increased atrial pressure which can produce a dilatation of the atria is an important predisposing factor in the production of the slow type of atrial fibrillation.

Since the above-described experiments suggested that the dilatation or stretch of the atrial muscle might be more important than the rise in intra-atrial pressure, a set of experiments was performed to illustrate that stretch alone could be responsible for changes in atrial muscle that account for the production of fibrillation. In vitro experiments were conducted on 5 rabbit left atria. The effective refractory period was determined by using supramaximal shocks (about 5 to 10 times threshold) and by finding the shortest interval in milliseconds, between the basal beat (1 per second) and a second beat introduced by means of a second stimulator The refractory period thus determined was usually between 30 and 50 milliseconds during control periods. The atria were then stretched and their refractory periods again determined. In 23 experiments with from 10 to 66 per cent stretch over the control length the refractory period shortened an average of 12 milliseconds (range of 5 to 25 milliseconds see Table II) The refractory period was determined as soon as possible after the muscle was stretched or relaxed There was an indication that if the muscle was allowed to accommodate to the newly stretched position the refractory period would tend to return in the direction of the pre-stretch values.

The experiments reported above were performed on animals in atrial flutter This arrhythmia provided a rapid continuous source of electrical activity in the atria which facilitated the production of atrial fibrillation Another series of experiments was designed to show that a single extrasystole under proper conditions of anoxia or asphyxia was capable of initiating a sustained atrial fibrillation. It is known[20,21] that one single strong shock applied to a dog atrium during its relative refractory period can initiate a short run of atrial fibrillation. Similar experiments were performed in dog atria which were driven electrically at rates just above the sinus rate. Shocks during any period of the cycle did not produce a persistent atrial fibrillation If the

Table II *Effects of stretch and relaxation on the refractory periods of isolated rabbit left atria*

Experiment number	*Length (cm.)*	*Effective refractory period (msec.)*
1	2.4	55
	3.0	40
	2.4	60
2	1.6	45
	2.2	30
	1.6	40
3	1.6	45
	2.6	30
	1.6	50
4	2.1	35
	2.7	20
	2.1	35
5	2.2	40
	2.8	25
	2.2	40

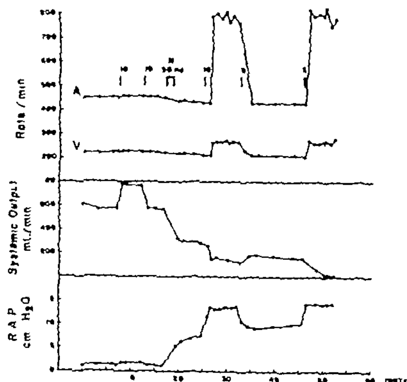


Fig. 6. The effect of increasing inflow pressure in producing a conversion of atrial flutter to fibrillation in the dog heart-lung preparation. +5 or +10, Raise inflow vessel 5 or 10 cm., respectively. *−5 or −10,* Lower inflow vessel to control (7 cm. above heart). *N,* Injection of 90 mg. of pentobarbital into inflow vessel. *A,* Atrial rate. *V,* Ventricular rate. *R.A.P.,* Right atrial pressure. Male dog, 18 kilograms.

strong shocks (15 volts and 5 milliseconds duration) were applied during the relative refractory period then occasionally a few discharges not exceeding 12 to 14 could be observed as a result of the single shock. If hypoxia was induced and atrial dilatation was beginning to become apparent, then a similar shock produced an atrial fibrillation which persisted as long as the animals were hypoxic and could be reverted by the reinstitution of air-breathing. This occurred in normal, vagotomized, and atropinized preparations (see Fig. 7).

Discussion

The findings described demonstrate that hypoxia, anoxia, or asphyxia are predisposing factors to the production of atrial fibrillation. It was also shown that a single extrasystole can produce a sustained atrial fibrillation during these conditions. Other work[22] has shown that atrial fibrillation once initiated can be sustained in the presence of increased vagal activity. Thus, it is likely that in the dog any factor that increases vagal activity by a direct or reflex action could predispose the animal to sustained fibrillation. Since atrial fibrillation occurs in the vagotomized atropinized heart, other factors besides vagal activity must be operative.

The results presented show that an increase in intra-atrial pressure which results in distention of the atrial walls, predisposed the atria to a slow type of fibrillation. These experiments also indicate that an increase in intra-atrial pressure per se is not the important factor; most likely it is the actual distention of the atria that plays the major role in predisposing the atria to fibrillation. Thus, it is understandable that in hypoxia or heart failure wherein a slight change in pressure can produce a marked distention of the atria the condition of atrial fibrillation is readily induced.

Vagal stimulation produces changes in the atrial refractory period which are not

uniform over the entire organ.[33] Evidence that fibrillation of the atria is most probably due to a number of wave fronts moving in an irregular fashion has been presented.[33] Thus the nonuniform changes produced by vagal stimulation can predispose the atria to the formation of an irregular wave front fragmentation and finally the production of multiple wave fronts. The findings presented herein are in agreement with those of other authors[1,23] who find that stretch of the atrial muscle predisposes to fibrillation. This may be explained in part by the finding presented above that stretch shortens the atrial refractory period and possibly changes patterns of conduction. It is also likely that stretch per se may result in either mechanical disruption of the conductile pathways or nonuniform changes in the refractory period across the atrium thereby predisposing the tissue to the formation of multiple wave fronts which is responsible for the production of fibrillation. The importance of an increase in the size of the atria in maintaining fibrillation has been stressed by Garrey.[34]

The effects of asphyxia or hypoxia in predisposing the atria to fibrillation have been shown to be due at least in part to changes in vagal activity and in the dilatation of the atrial chambers. Increased vagal activity caused by hypoxia could be due to a reflex activation of the carotid and aortic receptor areas. In this respect, the rise in blood pressure during hypoxia is a contributing factor since elimination of this rise in blood pressure by Dibenamine or SY 28 produced a consistent reduction in the maximal rate of atrial fibrillation which is seen with hypoxia. It is also likely that a reduction in the oxygen tension in the central nervous system is important as a cause of the vagal discharge, at least in the animals in which a rise in blood pressure was eliminated by an adrenergic blocking agent.

The findings that epinephrine or adrenergic discharge under the conditions of our experimental procedure did not significantly modify fibrillation by a direct action on the atria are not surprising in light of the work by other authors[8,24,25] which suggests that at least some if not all of the properties of the sympathetic amines are reduced or inhibited in the absence of oxygen.

Other factors which modify vagal activity may also be operative. It is known that the responses of the heart to direct or reflex vagal stimulation are increased during respiratory acidosis[30,31] and it has been suggested by these authors that a decrease in the activity of cholinesterase (optimal at pH 7.5 to 8.5) may be the responsible factor. Others[32-34] who found that

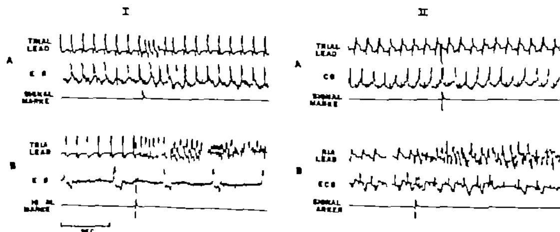


Fig. 7. Demonstration that single stimulus (20 volts and 5 milliseconds duration) applied during the relative refractory period of the atrial tissue will produce a sustained fibrillation during anoxia, both with the vagi intact (*I*) and cut (*II*). Recordings shown are similar sequences during (*A*) air-breathing and (*B*) nitrogen-breathing. Female dog, 14 kilograms. Atria were driven electrically [illegible] times faster than the sinus rate.

anemic or asphyxic dogs had an increased sensitivity to acetylcholine postulated that a decreased activity of cholinesterase may be playing a role

In vivo studies in dogs in which anoxic blood was perfused through the coronary arteries in the absence of cardiac distention demonstrated a predisposition to atrial fibrillation produced by a cholinergic agent.[1] This may be explained in part by the results of other studies in which a shortening of the rate of repolarization with anoxia alone has been shown on isolated preparations.[16]

Although hypercapnea has been shown to shorten the duration of the action potential[14] the results presented here do not show a conversion of atrial flutter to fibrillation with increased levels of carbon dioxide This does not exclude the possibility that the hypercapnea may in some way enhance this phenomenon when other factors are operating It is quite likely that other variables which occur during either acute or prolonged hypoxemia, such as electrolyte and hormonal imbalances may play a role in the production of atrial fibrillation

Summary

Asphyxia predisposes the atria to fibrillation of two types. The first is a rapid variety with a concomitant ventricular slowing which has been shown to be due to vagal discharge. The possible sources of this vagal activity have been studied

The second type is a slow fibrillation without ventricular slowing and is related primarily to distention of the atrial musculature A shortening of the refractory period by stretching of the atria has been demonstrated and it is suggested that this effect is a contributing factor in the production of this arrhythmia. An increase in the volume of the atria may be operative also.

The effect of single extrasystoles on the production of atrial fibrillation was studied. During control conditions a single shock produced a few extrasystoles, whereas under conditions of anoxia or asphyxia a similar shock produced persistent fibrillation in both the innervated and denervated preparations The conclusion is that under proper conditions a single extrasystole is enough to initiate an episode of sustained atrial fibrillation

REFERENCES

1. Smith J R. and Wilson, S: Studies on the production and maintenance of experimental auricular fibrillation Am Heart J 27:176, 1944
2. Brill I C and Meisner W A.: The role of coronary artery disease in the etiology of auricular fibrillation Ann Int. Med. 14:1341 1941
3. Levine, S A. Clinical heart disease ed. 3, Philadelphia, 1947 W B Saunders Company
4. Prinzmetal, M Corday E., Brill, I C., Oblath, R. W., and Kruger H E. The auricular arrhythmias Springfield, Ill., 1952, Charles C Thomas, Publisher
5. Farah, A. E. Some aspects of the physiology and pharmacology of experimental auricular flutter and fibrillation Proceedings of the Seventh Middle East Medical Assembly 1957 p. 166.
6. Swann, H G and Brucer M The cardiorespiratory and biochemical events during rapid anoxic death, Tex. Rep. Biol. & Med. 7:511 1949
7. Mautner H and Luisada A. Antagonistic effect of asphyxia to curare paralysis of the vagus nerve J Pharmacol. & Exper Therap. 72:386, 1941
8. Sands, J and DeGraff A C The effects of progressive anoxemia on the heart and circulation Am J Physiol. 74:416, 1925
9. Van Loo A Surtshin, A and Katz, L N: The nature of the two pressor responses to acute hypoxemia, with some observations on the role of the adrenals in hypoxemia Am. J Physiol. 154:397 1948.
10. Rosenblueth, A., and Garcia Ramos, J Studies on flutter and fibrillation. 2 The influence of artificial obstacles on experimental and auricular flutter Am. Heart J 33:677 1947
11. Scherf D Studies on auricular tachycardia caused by aconitine administration, Proc. Soc. Exper Biol. & Med 64:233, 1947
12. Fry F E. J A simple gas analyzer Am. J Res 27:188, 1949
13. Patterson, W S., and Starling, E. H On the mechanical factors which determine the output of the ventricles, J Physiol. 48:357 1914.
14a. Krayer O and Mendez, R.: The action of veratrine upon the isolated mammalian heart, J Pharmacol. & Exper Therap. 74:350, 1942
14. Farah, A., and Birnbaum L.: Decelerator and anti-arrhythmic properties of amotriphene, J Pharmacol. & Exper Therap. 127:128, 1959.
15. Scherf D The effect of sympathetic stimulation on auricular flutter Am. Heart J 37:1069 1949
16. Aviado, D M., Jr and Schmidt, C. F: Reflexes from stretch receptors in blood vessels, heart and lungs, Physiol. Rev 35:247 1955
17. Luten, D and Jeffreys, E. O: The clinical significance of auricular fibrillation J A.M A. 107:2079 1936.
18. Luten, D: The relationship of tachycardia to

cardiac insufficiency Am. Heart J 12:435 1936.

19 Master A. M., Dack, S., and Jaffe, H L. Disturbances of rate and rhythm in acute coronary artery thrombosis, Ann. Int. Med. 11 735, 1937

20 Orias, O Gilbert, J L., Siebens, A. A., Suckling E. E., and Brooks, C.: Effectiveness of single rectangular electrical pulses of known duration and strength in evoking auricular fibrillation, Am. J Physiol. 162:219 1950.

21. Andrus, E. C., Carter E. P., and Wheeler H A. The refractory period of the normally beating dog auricle with a note on the occurrence of auricular fibrillation following a single stimulus, J Exper Med. 51:357 1930.

22. Moe, G. K., and Abildskov J A. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge, Am. Heart J 58:59 1959

23 Alessi, R., Nusynowitz, M Abildskov J A., and Moe, G. K. Nonuniform distribution of vagal effects on the atrial refractory period, Am. J Physiol. 194:406 1958.

24 Scherf D and Schott, A. Extrasystoles and allied arrhythmias, London, 1953, Heinemann.

25. Garrey W E. The nature of fibrillatory contraction of the heart—its relation to tissue mass and form, Am. J Physiol. 33:397 1914.

26. Acheson, G. H Farah, A and French, G N Some effects of Dibenamine on the mammalian heart, J Pharmacol & Exper Therap 97:455 1949

27 Blaschko, H., Richter D and Schlossmann, H. Oxidation of adrenaline and other amines Biochem. J 31:2187 1937

28. Van Loo, A., Rodbard S., and Katz, L. N Inhibition of epinephrine action in severe hypoxemia, Am. J Physiol. 152:623, 1948.

29 Ellis, S. The influence of enzyme inhibitors on the action of epinephrine on the frog's heart, J Pharmacol. & Exper Therap. 105:381, 1952.

30. Sloan, H E. The vagus nerve in cardiac arrest, Surg Gynec. & Obst. 91:257 1950

31 Young, W G Jr Sealy W C., Harris, J and Botwin A. The effects of hypercapnea and hypoxia on the response of the heart to vagal stimulation, Surg Gynec. & Obst 93:51 1951

32 Horlick, L., and Surtshin, A. The role of anemia in the experimental production of heart block and auricular fibrillation in the dog Am. Heart J 38 716, 1949

33 Callebaut, C. Rodbard, S., and Katz, L. N Sensitivity of the supraventricular pacemakers to acetylcholine in acute hypoxemia, Circulation 1 712, 1950

34. Richard, A Action de l'asphyxie sur la cardio-inhibition vagale, Ann. de physiol. 12 774, 1936.

35. Webb, J L., and Hollander P B The action of acetylcholine and epinephrine on cellular membrane potentials and contractility of rat atrium Circulation Res. 4:332, 1956.

36. Coraboeuf, E., and Boistel, J L action des taux élevés de gaz carbonique sur le tissu cardiac étudiée à l aide de micro-electrodes intracellulaires, Compt. rend soc. biol. 147:654 1953.

The mechanism of arrhythmias during insulin induced hypoglycemia

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The possible danger of hypoglycemia in patients with arteriosclerosis was anticipated by Joslin in 1930 Shortly afterward papers which described the occurrence of angina pectoris[2,4] and myocardial infarction[3] in diabetic patients after insulin-induced hypoglycemia were published Some of these early papers have been criticized for their lack of detail [6] and recent studies have shown that hy kalemia rather than ischemia is responsible for the electrocardiographic changes which may occur [6-9] For example a study by Judson and Hollander[8] of 11 patients with ischemic heart disease showed that the electrocardiographic changes induced by hypoglycemia due to insulin were distinct from those produced by standard exercise tolerance tests in the same patients. It seems reasonably certain therefore from these studies that hypokalemia contributes very largely to the RS-T and T wave changes which occur in hypoglycemia. Several studies[4,5,3] refer to the incidence of arrhythmias during insulin-induced hypoglycemia, and it seems to us from the present study of a patient in whom serial electrocardiograms, blood sugar serum potassium and urinary excretion rates of catecholamines are available during an insulin-induced arrhythmia that other factors beside a low serum potassium may be involved

Case report

This patient 54-year-old Negro woman wa treated with radioactive iodine for thyrotoxicosis in 1953 The following year she was found to ha e developed postirradiation myxedema, and since then she had been maintained on continuous medication w th th roid of one form or another Since 1955 her blood pressure has been mildly elevated, to about 160-170/100 mm Hg, but her fundi have remained normal and there has been no cardiac enlargement Twelve-lead electrocardiograms h e been taken at about monthl intervals since 1958, and these show left entricular hypertrophy It is noteworthy that in 22 such records which are a ailable not a single ventricular extrasystole has ever been recorded, and the patient has never complained of palpitations. During the past year the patient has been one of a group of patients maintained euthyroid on sodium dextrothyroxine, at a dose of 10 to 12 milligrams daily As part of a series of current studies, a modified adrenal medullary function test was performed This consisted of a standard insulin t lerance test during which the urinary excretion of catecholamines was estimated. In addition Lead aVL was taken throughout the test, in order to record anticipated changes in the left entricular complex. On the day of the test the basal metabolic rate (BMR) was −4 per cent cholesterol was 235 mg per cent, and the resting electrocardiogram (ECG) (Fig 1) showed left entricular hypertrophy The Achilles tendon reflex was measured several times and a eraged 280 milliseconds, which is normal. The serum protein bound iodine (PBI) was 12.6 µg per cent which is

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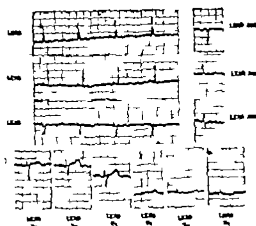


Fig. 1 Third 6-lead electrocardiogram taken immediately before the insulin tolerance test

compatible with euthyroidism in a patient on dextrothyroxine

The events which occurred during the insulin tolerance test are summarized in Fig. 2. A dose of 0.1 units of insulin per kilogram of body weight was given intravenously and at this time the blood sugar was 82 mg. per cent, serum potassium was 4.2 mEq./L., the heart rate was 63 per minute, the blood pressure was 175/105 mm. Hg, and the T wave in the ECG was upright (Fig. 3,A). Fifteen minutes later the blood sugar had fallen to 30 mg. per cent, serum potassium was 4.1 mEq./L., the heart rate was 60 per minute, the blood pressure was 180/110 mm. Hg, and the T wave had become diphasic (Fig. 3,B). At 30 minutes the pulse rate had increased to 74 per minute, the blood pressure was 190/110 mm. Hg, the blood sugar had risen to 46 mg. per cent, and the serum potassium had fallen to 3.1 mEq./L. The patient was sweating. The ECG showed inversion of the T wave and the presence of a U wave (Fig. 3,C). Very soon after this the patient felt dizzy. She had an irregular pulse, and the ECG showed frequent ventricular extrasystoles (Fig. 3,D). An intravenous injection of 20 c.c. of 50 per cent glucose was given, and toward the end of the injection, i.e., about 4 minutes later, normal sinus rhythm had been restored (Fig. 3,E). The RS-T and T waves appeared to be very similar to those recorded immediately before the onset of the arrhythmia. Nine minutes later the ECG was very much like the control reading (Fig. 3,F), although the serum potassium was still 3.1 mEq./L., whereas the blood sugar had risen to 111 mg. per cent. During the next one and a quarter hours the blood sugar returned to 83 mg. per cent, the serum potassium rose to 4.2 mEq./L., and there was little change in the ECG (Fig. 3,G and H).

A control 1 hour collection of urine prior to the test, indicated an epinephrine excretion rate of 1.03 μg per hour. Within the 35 minutes after the injection of the insulin until the correction of the arrhythmia, the urinary excretion rate was 4.51 μg per hour; during the next 25 minutes it was 3.06 μg per hour, and during the following 1-hour period of recovery it was 2.18 μg per hour. The rates for norepinephrine were 1.36, [illegible], 0.10, and 1.51 μg per hour, respectively. (Free unhydrolyzed epinephrine and norepinephrine were determined by adsorption on Amberlite CG-50, elution with acetic acid, oxidation, and tautomerization to form lutins. Differential fluorometry was used to distinguish between epinephrine and norepinephrine.)

Discussion

The absence of clinical symptoms of hypothyroidism and the normal BMR, serum cholesterol, PBI, and Achilles tendon reflex suggest that this patient was euthyroid at the time of the insulin tolerance test. A moderate degree of hypokalemia occurred during the tolerance test and was probably responsible for the T wave changes in the 15 and 30-minute electrocardiograms, and also for the appearance of the U wave at 30 minutes. When normal sinus rhythm was restored after intravenous glucose, these hypokalemic electrocardiographic changes were still present, but 10 minutes later, when repeat serum estima

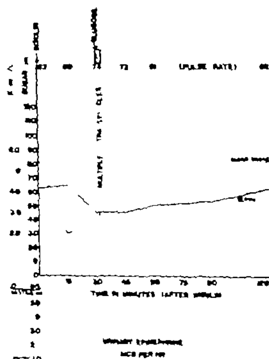


Fig. 2 Summary of changes in the blood sugar, serum potassium, urinary excretion of epinephrine, and the pulse rate which occurred during the insulin tolerance test. The multiple extrasystoles ceased during injection of glucose which lasted 3 to 4 minutes.

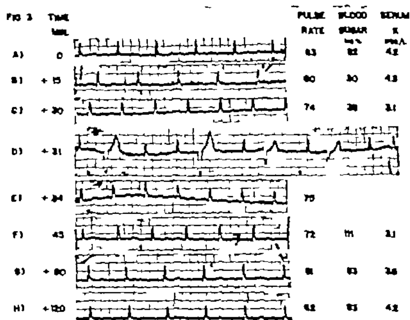


Fig. 3. Electrocardiograms (Lead aVL) taken during the insulin tolerance test are compared with the changes in the blood sugar and serum potassium (time in minutes from the injection of insulin).

tions showed a persistently low serum potassium the electrocardiogram had returned almost to the control form According to Surawicz and Lepeschkin[11] the hypokalemic RS-T and T wave changes are probably related to the potassium gradient across the cell membrane and not to the extracellular or intracellular concentrations of potassium and this gradient in our patient may have been influenced by the correction of the hypoglycemia. However the electrocardiogram recorded immediately after the arrhythmia was controlled would suggest that the cellular potassium gradient was still abnormal and therefore it is unlikely that changes in potassium were alone responsible for the arrhythmia. Hypokalemia itself does not appear to produce cardiac arrhythmias in patients until the level of potassium in the serum has fallen below 2 6 mEq /L.[11] and in the experimental animal pure potassium loss, induced by hemodialysis, sufficient to reduce the serum level to 2 mEq./L. did not produce an arrhythmia [12] It seems possible, therefore that hypokalemia is often associated with arrhythmias because it makes the heart more sensitive to other agents which are capable of inducing them It has been shown for example that reduction of the serum potassium by hemodialysis in digitalized patients may precipitate digitalis-induced arrhythmias [12] and in the treatment of congestive cardiac failure the association of hypokalemia with digitalis-induced arrhythmias is well known.[14] In the case reported here a factor which must be seriously considered as the cause of the arrhythmia is epinephrine which is a potent cause of cardiac arrhythmias especially ectopic beats [15] and the secretion of which is greatly increased during insulin induced hypoglycemia.[16] If epinephrine were maintaining the arrhythmia in the present case a rapid fall in its concentration should cause a reversion to normal rhythm and one must therefore inquire whether the intravenous injection of glucose is capable of rapidly reducing the secretion of epinephrine. Duner [17] studying the cathecholamine content of adrenal venous blood in the cat, showed that the secretion of epinephrine fell rapidly after the intravenous injection of glucose and Bethune and associates[18] stated that in dogs which had been made hypoglycemic by insulin the epinephrine content of the adrenal venous blood fell abruptly when glucose was infused. It seems very probable therefore, that a con-

siderable reduction in the adrenal production of epinephrine occurred in this patient during the 4-minute period when glucose was being injected this is confirmed by the reduction by one third of the rate of excretion of adrenaline in the urine in the 25-minute period after injection of glucose

It is suggested therefore from the evidence available in this case that some of the arrhythmias which occur apparently not uncommonly during insulin induced hypoglycemia may be due to the action of epinephrine on a heart which is abnormally sensitive as a result of the hypokalemia which normally accompanies this type of hypoglycemia. Certain of these arrhythmias may be rapidly corrected at first by glucose but if uncontrolled they may contribute to the deaths from myocardial infarction which has been reported to follow insulin-induced hypoglycemia.[19,20]

Summary

A standard insulin tolerance test was carried out on a fully treated hypothyroid patient About 30 minutes after the injection of insulin the patient developed multiple ventricular extrasystoles, which were controlled within 4 minutes of an intravenous injection of glucose Blood sugar serum potassium and the urinary excretion of catecholamines were measured during the control period and for 2 hours after the injection of insulin From this evidence it is suggested that the commonly occurring arrhythmias of insulin-induced hypoglycemia may be caused by the action of epinephrine on a heart which is abnormally sensitive as a result of the hypokalemia which normally accompanies hypoglycemia. The intravenous injection of glucose may correct the arrhythmia by causing an abrupt fall in the adrenal secretion of epinephrine

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REFERENCES

1 Joslin, E P Arteriosclerosis in diabetes. Ann Int Med. 4:54 1930
2. Turner K B Insulin shock as the cause of cardiac pain, Am Heart J 5:671 1930.
3 Modern, F S Chronic heart pain due to prolonged hypoglycemia J A M A 96:357 1931.
4 Strouse, S., Soskin, S., Katz, L. N and Rubinfeld S. H Treatment of older diabetic patients with cardiovascular disease, J.A M A. 98 1703 1932
5. Parsonnet, A. E and Hyman, A S. The development of the stenocardial syndrome following the administration of insulin in diabetics with coronary thrombosis, Ann. Int Med. 4:1247 1931
6. Egeli, E. S and Berkmen, R Action of hypoglycemia on coronary insufficiency and mechanism of ECG alterations Am Heart J 59:527 1960
7 Parrish, A E., Sugar S. J N and Fazekas, J F A relationship between electrocardiographic changes and hypokalemia in insulin-induced hypoglycemia, Am Heart J 44:815 1952
8 Judson, W E and Hollander W Effects of insulin-induced hypoglycemia in patients with angina pectoris, Am Heart J 52 198, 1956
9 Broustet, P and Traneur, M Le glucose dans les manifestations cardiaques des hypoglycemies, Prog Med (Paris) 89 184 1961
10. Brunjes, S Hodgman, J E., Nowack, J and Johns, V J An adrenal medullary function test Ann. Int. Med. 54:1045 1961
11 Surawicz, B and Lepeschkin, E. Electrocardiographic pattern of hypopotassemia with and without hypocalcemia Circulation 8:801 1953
12. Weller J M Lown, B Hoigne R V Wyatt, N F Criscitiello M Merrill, J P and Levine S A. Effects of acute removal of potassium from dogs. Changes in the electrocardiogram Circulation 11:44 1955
13 Kohn, R M and Kiley J E Electrocardiographic changes during hemodialysis with observations on the contribution of electrolyte disturbances to digitalis toxicity Ann Int Med 39 38 1953
14 Lown B and Levine, S A Current concepts of digitalis therapy Boston 1954 Little Brown & Company
15 Lepeschkin, E Marchet H Schroeder G Wagner R de Paula Silva P and Raab, W Effect of epinephrine and norepinephrine on the electrocardiograms of 100 normal subjects, Am J Cardiol 5:594 1960
16 Euler U S von, and Luft R. Effect of insulin on urinary excretion of adrenalin and noradrenalin Metabolism 1:528 1952
17 Duner H The influence of the blood glucose level on the secretion of adrenaline and noradrenaline from the suprarenal, Acta physiol. scandinav 28 Suppl. 102, 1953.
18. Bethune, J E Goldfien A Zileli, M S and Despointes, R. H Effect of hypoglycemia and amphenone on adrenal secretion of epinephrine and norepinephrine, Fed Proc 16 11 1957
19 Gilbert, R A and Goldzieher J W Mechanism and prevention of cardiovascular changes due to insulin, Ann Int Med. 25:928 1946
20 Gandevia, B. The association between hypoglycemia and myocardial infarction Med J Australia 1:33, 1954.

Case reports

External countershock treatment of ventricular fibrillation and tachycardia

A case report

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During the past few years there have been revolutionary developments in the techniques of cardiac resuscitation. Paramount in these advancements has been the use of electrical current to terminate ventricular fibrillation and to serve as a cardiac pacemaker. Recently,[1-3] this form of treatment has been applied to the management of other serious cardiac arrhythmias, especially ventricular tachycardia. This case report is presented to demonstrate the effectiveness of present-day closed-chest techniques of cardiac resuscitation and to stress the value of electrical countershock therapy in the management of ventricular tachycardia which has proved resistant to all other forms of treatment.

Although suggested in 1775,[4] the possibilities of electrical therapy of cardiac arrhythmias lay dormant for many years and were finally awakened at the turn of the twentieth century by investigations[5-7] that actually demonstrated the effectiveness of electrical current in influencing cardiac rhythm. By 1937 its clinical application in the treatment of ventricular fibrillation was established by Beck and Mautz.[8,9] In the past decade open-chest cardiac massage and defibrillation of the exposed heart by countershock became standard practice. The necessity of thoracotomy to carry out these resuscitative procedures has been a limiting factor in their success. The importance of the time factor, which requires prompt decision and action, has led to thoracotomy in some instances in which less radical measures would have sufficed. The necessity of thoracotomy performed under less than ideal circumstances has also led to complications which have resulted in mortality or serious morbidity.[1] Thus, the need for the development of a technique that would eliminate the requirement for thoracotomy was recognized[1,12] at the very time when the open-chest approach was being perfected and accepted as the correct procedure in the treatment of ventricular fibrillation. A major advance toward closed-chest cardiac resuscitation was the development primarily by Zoll[14] of an external electrical pacemaker in instances of cardiac arrest or ventricular standstill in the Adams-Stokes syndrome. Supported by these achievements, Zoll[14] and others[15] perfected the means of external countershock therapy of ventricular fibrillation. The technique of closed-chest cardiac massage[16] developed by the group at The Johns Hopkins Hospital was the counterpart that made

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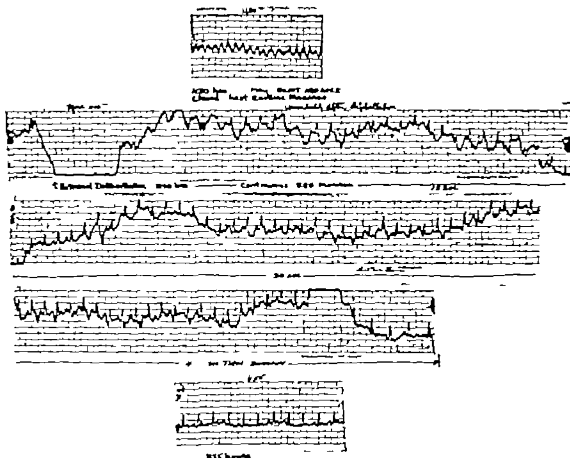


Fig. 1 Electrocardiographic monitoring during the episode of ventricular fibrillation and including the period of external electrical countershock therapy. The representative tracing obtained during the 20-minute period of external cardiac massage demonstrates the ventricular fibrillation. The time of countershock is indicated, and the conversion of the ventricular arrhythmia to supraventricular arrhythmia, probably atrial tachycardia with variable atrioventricular block, is demonstrated. Subsequently this arrhythmia proved to be of only brief duration, with spontaneous conversion to a normal sinus rhythm, and the appearance of multifocal premature ventricular contractions (Fig. 2).

closed-chest cardiac resuscitation possible and effective. Work has also progressed in the application of electrical techniques to the treatment of other serious cardiac arrhythmias and countershock therapy in the management of resistant ventricular tachycardia has been successful.[3] It is the application of this technique that is emphasized in the following case report.

Case report

This 40-year-old man had no cardiovascular symptoms prior to an acute myocardial infarction of the anterior wall on Nov. 30, 1960. His course of convalescence was complicated by several episodes consistent with a postmyocardial infarction syndrome. On April 23, 1961, a posterior myocardial infarction occurred. Because of an intermittent pericardial friction rub, anticoagulation therapy was not instituted. Convalescence from this episode was otherwise without complications until 11 A.M. on May 22, 1961, when the patient had a syncopal episode of a few seconds duration while he was seated in a wheelchair in the x-ray department. Approximately 2 minutes later a second syncopal episode occurred and he became cyanotic and pulseless. External cardiac massage and mouth-to-mouth breathing were immediately instituted. An electrocardiogram showed ventricular fibrillation (Fig. 1). Several episodes of emesis occurred during the period of external cardiac massage. An endotracheal tube was then inserted, and, after tracheal suction, bag breathing with oxygen was begun. These resuscitative measures were continued for approximately 30 minutes, until defibrillation was successfully performed by external

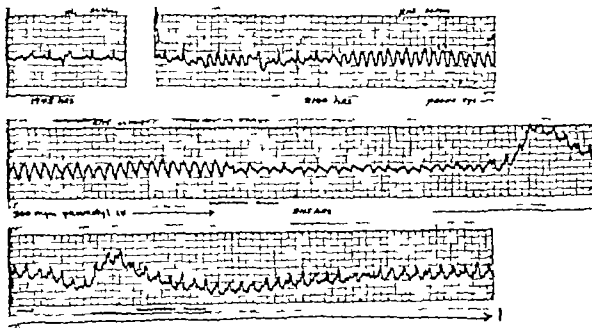


Fig 2 Electrocardiograms documenting the progression from a normal sinus rhythm with multifocal premature ventricular contractions to a persistent ventricular tachycardia with a rate of 200 per minute. Note the development of a transient episode of probable ventricular flutter during the early period of therapy with intravenous procaine amide and the resumption of ventricular tachycardia at another focus with a rate of 180 per minute.

countershock, with conversion to an atrial tachycardia with variable block (Fig 1), and then a normal sinus rhythm with frequent multiple premature ventricular contractions.

After defibrillation, the blood pressure was 96/60 mm. Hg; it rose to 110/88 mm. Hg after he was given 5 mg. of Metaraminol intramuscularly. Physical examination at that time revealed no significant changes from an evaluation which was made just prior to the episode, and which had demonstrated only mild cardiomegaly and an intermittent pericardial friction rub. There was no evidence of congestive heart failure. Serial electrocardiograms and laboratory studies were suggestive of myocardial necrosis, and recurrent myocardial infarction was suspected even though electrocardiographic changes were not diagnostic.

After conversion to sinus rhythm, the patient received 200 mg. of procaine amide intravenously and was placed on oral quinidine sulfate 400 mg. every 6 hours because of multifocal premature ventricular contractions. That afternoon he required repeated injections of morphine sulfate for pain in the chest. At 9 P.M. ventricular tachycardia developed at a rate of 200 per minute (Fig 2). Pressor amines were required to maintain blood pressure. By 10 A.M. the following day the patient had received 3,050 mg. of procaine amide intravenously in an unsuccessful attempt to effect conversion of the arrhythmia. Thereafter oral quinidine sulfate therapy was increased to 600 mg. every 4 hours.

At noon on May 23, 1961, the heart converted to a sinus rhythm with multiple premature ventricular contractions. At the same time severe pulmonary edema developed; this necessitated rapid digitalization, rotating tourniquets, intermittent positive pressure breathing and phlebotomy for control. Congestive failure gradually improved, although multifocal premature ventricular contractions continued until 3 P.M. on May 24 when ventricular tachycardia recurred with a rate of 200 per minute. An infusion of levarterenol bitartrate was again required to maintain the blood pressure in the range of 100/60 mm. Hg. The patient was given 2,600 mg. of procaine amide intravenously over a 2-hour period, with a slowing of the ventricular rate to 160 per minute but without conversion. Intensive oral quinidine and Atabrine therapy were also unsuccessful and were discontinued. Intramuscular quinidine gluconate, 400 mg. every 2 hours, was then instituted; a total dosage of 2.8 Gm. was given over the next 12 hours, without conversion. All quinidine therapy was discontinued at noon on May 25.

Because it was thought that an inflammatory focus might be giving rise to the arrhythmia, he was given 100 mg. of hydrocortisone sodium succinate intravenously on May 25, and was started on oral dexamethasone therapy which was maintained at 3.75 mg. every 6 hours for the next 3 days. That same day he developed pneumonitis of the right upper lobe. Improvement was prompt on appropriate antibiotic therapy, and the evidence of pneumonitis disappeared in the subsequent 5 days.

On the morning of May 26, shortly after midnight, the heart transiently converted to a sinus rhythm with frequent multifocal premature ventricular contractions. At that time, 600 mg. of quinidine sulfate by mouth every 4 hours was reinstituted. Throughout the day the episodes of ven-

tricular tachycardia gradually increased in frequency and duration. A test of the level of quinidine in the blood showed 11.05 mg. of quinidine base per liter of serum. Because of a progressive increase of over 30 per cent in the QRS duration, quinidine was discontinued. Ventricular tachycardia became constant at 7:20 P.M., and increased to a rate of 200 per minute by the next morning. Because of deterioration of the patient's clinical status, marked by signs of progressive congestive failure, falling blood pressure despite intravenous pressor amines, the development of disorientation, and a failure to respond to intensive antiarrhythmic drug therapy, conversion of the ventricular tachycardia by countershock was considered to be essential.

After approximately 19 hours of continuous ventricular tachycardia and 5 days during which the arrhythmia was almost continuous, the first countershock was given with the patient under light anesthesia with intravenous Pentothal sodium and nitrous oxide. At 2:30 P.M. on May 27 the defibrillator sent through the chest a 60-c.p.s. AC current of 5 amperes for one-fourth second at a potential of 440 volts. After the countershock, the heart initially converted to a sinus rhythm, as illustrated in Fig. 3. However, runs of ventricular tachycardia again appeared, and 300 mg. of procaine amide given intravenously between 2:45 and 2:55 P.M. did not prevent the reappearance of sustained ventricular tachycardia by 3:08 P.M. At that time he was given a second countershock (Fig. 4), with conversion to a sinus rhythm, but soon thereafter runs of ventricular tachycardia appeared, and the third and final countershock was given at 3:10 P.M. After this final shock, basic normal sinus rhythm persisted (Fig. 4), although there were frequent multifocal premature ventricular beats and occasional intermittent runs of ventricular tachycardia which lasted for 3 to 4 seconds. This rhythm continued for the next 24 hours. The patient's general condition appeared to be much improved. The blood pressure remained within normal limits without the aid of vasopressors. After the countershock therapy, he was placed on oral doses of procaine amide, 750 mg., and quinidine sulfate, 0.4 Gm. every 6 hours, potassium chloride, 1 Gm. every 6 hours, and digoxin, 0.25 mg. twice daily. Between May 28 and May 31 the patient had several very transient episodes of ventricular tachycardia. Thereafter, continued improvement in his condition was evident, with eventual ambulation. However, since countershock treatment there have been intermittent recurrences of the postmyocardial infarction syndrome and one episode suggestive of a recurrent myocardial infarction. Except for occasional premature ven-

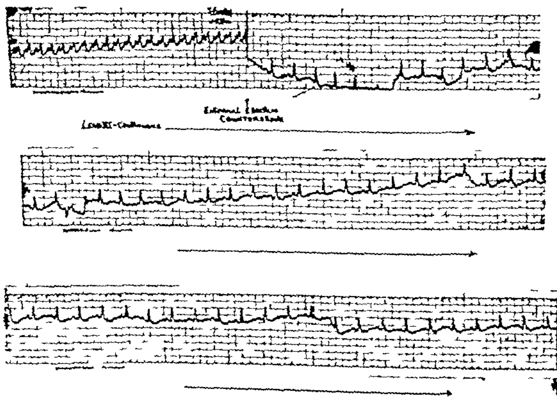


Fig. 3. Record of continuous electrocardiographic monitoring with Standard Lead III during initial external countershock therapy of ventricular tachycardia. Note the immediate conversion from the ventricular tachycardia with a rate of 200 per minute to a sinus rhythm with a rate of 90 per minute.

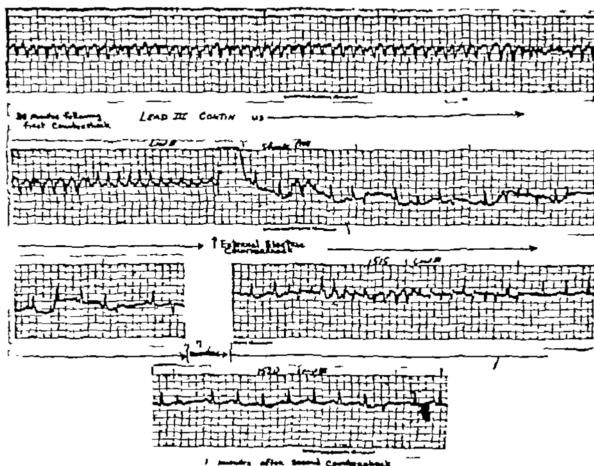


Fig. 4. Thirty-eight minutes after the initial countershock therapy of ventricular tachycardia the resulting normal sinus rhythm with increasingly frequent multifocal premature ventricular contractions once again develops into the sustained ventricular arrhythmia. This ventricular tachycardia is characterized by multiple ectopic ventricular foci, and three of these are identifiable in the electrocardiogram monitored just prior to the second external electrical countershock treatment. Although prompt conversion to a normal sinus rhythm occurred with treatment, multifocal premature ventricular contractions and short runs of ventricular tachycardia persisted. A third countershock treatment (not illustrated) was given. It resulted in a normal sinus rhythm with only an occasional premature ventricular contraction.

tricular contractions, the heart has maintained a normal sinus rhythm for 6 months after countershock therapy.

Comment

The ability of the heart to return to a normal sinus rhythm after prolonged ventricular fibrillation may be expected as long as an effective circulation is maintained. It is important to emphasize this point, for it is obvious that outside the well-equipped operating room the chance of obtaining proper equipment for external defibrillation before the lapse of a quarter of an hour or even longer is remote. With proper resuscitative procedures, now devoid of the necessity of thoracotomy, the cardiorespiratory mechanism may be maintained for the necessary time to obtain the proper equipment.

Of particular interest is the ability of external electrical countershock therapy to provide an effective treatment of intractable ventricular tachycardia. In the reports of the treatment of ventricular tachycardia there are a few patients in almost every series who prove to be refractory to all medication. Admittedly, in some patients no form of therapy will be adequate to compensate for the severe myocardial damage that a specific disease process has produced. Nevertheless, one

cannot predict with certainty the extent of a pathologic process that has led to an apparently intractable arrhythmia. Thus, in those individuals whose ventricular tachycardia has not responded to the usual drug therapy and in whom toxic effects are serious or when the effects of the drugs may be contraindicated as in the patient with known complete atrioventricular block, the new approach of external countershock therapy should be used. Countershock must be carried out with proper equipment [n] and with proper placement of the electrodes at the suprasternal notch and at the cardiac apex. Because of pain the countershock should be performed under minimal anesthesia with agents which have no significant cardiotoxic effect. Hypoxia must be avoided.

Ventricular fibrillation or cardiac standstill may result from countershock therapy of ventricular tachycardia. Consequently electrocardiographic monitoring is necessary immediately after the shock so that appropriate procedures may be instituted promptly to restore effective heart action. An external electrical pacemaker must be available immediately should standstill occur and immediate repeat countershock must be applied should ventricular fibrillation result.

One might attribute the correction of either of these serious ventricular arrhythmias to changes in cellular ionic or electrical phenomena suddenly altered by an electrical current of this magnitude. Although the exact mechanism may be speculative, it is reasonable to assume that an immediate depolarization of the entire myocardium results, but a prolonged effect on the cardiac rhythmicity would be more difficult to explain. Therefore it is intriguing to theorize that this patient may have derived a sustained beneficial effect even though we recognize the fact that he received antiarrhythmic drugs after countershock. It is significant that control of the ventricular tachycardia was not possible by the same antiarrhythmic drugs in much larger dosages prior to the countershock. Although this particular thought of a sustained benefit is speculation, it is evident that this form of therapy holds promise of being an effective and less deleterious therapeutic approach to the more serious cardiac arrhythmias and is worthy of continued evaluation.

Conclusion

Maintenance of effective cardiopulmonary function with closed-chest techniques of resuscitation has proved adequate for a period sufficiently long to allow more complicated methods of treatment to be brought into operation. Not only has external electrical countershock terminated ventricular fibrillation it has also proved effective in the management of drug refractory ventricular tachycardia.

We wish to express our appreciation to Dr Bernard Lown, who was consulted in the management of this patient.

REFERENCES

1 Zoll, P M Linenthal, A J and Zarsky L R. N Ventricular fibrillation. Treatment and prevention by external electric current, New England J Med. 262 105 1960
2 Clarebrough J K., and Hopkins, I Control of entricular tachycardia by direct cardiac electric shock, Circulation 23:925, 1961
3. Alexander S Kleiger R and Lown, B Use of external electric countershock in the treatment of entricular tachycardia, J A M.A. 177:916, 1961
4. Abildgaard C. P Cited by Mackay R S., and Leeds, S. E Physiological effects of condenser discharges with application to tissue stimulation and ventricular defibrillation, J Appl. Physiol. 6:67 1953
5 Prevost and Batelli Cited by Ferris, L King, B G Spencer P W and Williams, H. B Effect of electrical shock on the heart, Electrical Engineering 55:498 1936.
6 Hyman, A S. Cited by Callaghan, J C., and Bigelow W G An electrical artificial pacemaker for standstill of the heart, Ann. Surg. 134:8, 1951
7 Hooker D R Kouwenhoven W B and Longworthy O R. The effect of alternating electric currents on the heart, Am. J Physiol. 103:444 1933
8 Beck, C. S., and Mautz, F R The control of the heart beat by the surgeon with reference to ventricular fibrillation occurring during operation Ann Surg 106:532 1937
9 Beck, C S Resuscitation for cardiac standstill and entricular fibrillation occurring during operation Am. J Surg 54:273 1941
10. Straight, W M Litwak, R., nd Turner J C J Sudden death in acute myocardial infarction report of a case with observations on the cause, prevention, and management, Ann. Int Med. 54:566, 1961
11 Gurvich, N L and Yunyev G. S. Restoration of heart rhythm in the [illegible] fibrillating heart, Am Rev Soviet [illegible]
12 Guyton, A. C., nd [illegible]

cerned in electrical defibrillation of the heart, particularly through the unopened chest Am J Physiol. 167:81 1951
13 Kouwenhoven W B Jude J R and Knickerbocker G G Heart activation in cardiac arrest, Mod Concepts Cardiovas. Dis. 30:639 1961
14 Zoll, P M Resuscitation of the heart in ventricular standstill by external electric stimulation New England J Med 247 768, 1952.
15 Zoll P M Linenthal, A. J Gibson W., Milton H P and Norman, L. R.: Termination of ventricular fibrillation in man by externally applied electric countershock, New England J Med 254:727 1956.
16. Kouwenhoven, W B Jude, J R. and Knickerbocker G G Closed chest cardiac massage J.A.M A 173:1064 1960.

Levocardia with partial situs inversus, an incidental finding in a 15-year-old boy

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Levocardia with abdominal situs inversus is a rare condition. Campbell and Forgacs[4] reported 14 cases and collected 19 others from the literature between 1947 and 1953. Keith[9] collected 62 cases which were verified by postmortem examination and added 4 of his own. Nadas[15] encountered 11 cases of this anomaly during the period from 1947 to 1957. It is estimated that this condition occurs in 1 per cent of the cases of congenital heart disease.[9]

Since it is commonly associated with severe and multiple cardiac malformations, levocardia with transposed abdominal viscera results in cyanosis, severe disability, and high mortality in infancy.[1,7,9,1] Only 5 per cent of these patients survive more than 5 years.[9] Most of the small number of adult patients reported upon were severely disabled.

Levocardia, as an incidental finding in adults seems to be very rare. Campbell reported the case of a 32-year-old symptomless man with levocardia in whom an inconstant murmur of aortic insufficiency and x-ray evidence of hypertrophy of the left side of the heart were the only cardiac abnormalities found.[2, Case 1] In 1829 Bujalski described the case of a 42-year-old man with levocardia who died after strangulation of the omentum. Toldt's case (1899) was that of a 40-year-old woman with partial situs inversus. In 1942 Carache described the case of a 49-year-old man with levocardia and abdominal situs inversus who died from lymphosarcoma (quoted by Putschar[18]).

We report here the incidental finding of levocardia in a 15-year-old boy who also showed unusual lobation of the lungs and possibly some features of Marfan's syndrome.

Case report

A. R., a 15-year-old Jewish boy of Persian origin, a carpenter's apprentice, was hospitalized for observation after a minor cranial trauma. He denied any previous discomfort on physical effort and had no knowledge of any cardiac abnormality. He was a small thin boy with kyphoscoliosis, marked pectus excavatum, and flat feet. His habitus was suggestive of the Marfan syndrome. Body measurements are recorded in Table I. His forehead seemed large and out of proportion to the rest of his face; the chin was particularly small and receding, which caused marked malocclusion of the teeth. The palate was high arched. The pupils were round and equal, reacting to light and accommodation. The fundi were normal. No dislocation of the lens was found by slit-lamp examination.

There was no dyspnea or cyanosis nor were the neck veins distended. The apex impulse could not be definitely located by palpation because of the thoracic deformity. No thrill was felt. On auscultation, the first heart sound at the apex was not unusual. The second sound at the pulmonary area was of normal intensity. There was a Grade 4 (in a scale of 6) systolic murmur which was heard best above

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Fig. 1. Normal cardiac silhouette. The stomach is located on the right.

the left border of the heart, the left infraclavicular region, and the axilla. The murmur began immediately after the first sound and occupied the entire systole. It was widely propagated and audible over the entire precordium, the right side of the chest, the neck, and the back. No diastolic murmur or third heart sound was heard.

The left lower thorax was dull to percussion anterolaterally. The liver and spleen could not be palpated. The lungs were clear to percussion and auscultation. Blood pressure was 105/65 mm. Hg in the arm and 120/75 mm. Hg in the leg. On fluoroscopic examination the cardiac silhouette appeared to be normal, and barium swallow revealed that the stomach was located on the right (Fig. 1). Tomography and bronchography showed that each lung consisted of two lobes (Fig. 2). Additional x-ray studies showed that the liver and gall bladder were located on the left side (Fig. 3). Barium enema revealed that the large intestine was normally placed: the sigmoid and descending colon were on the left, and the cecum on the right, and it was possible to dislocate the left flexure toward the right side of the abdomen, indicating a long mesocolon.

The electrocardiogram (Fig. 4) showed an incomplete right bundle branch block with an rsR_1S_1 pattern in Lead V.[4] The vectorcardiographic examination gave the following findings: In the horizontal plane most of the QRS loop was in the anterior field; the centripetal arm of the loop was directed clockwise. In the sagittal plane most of the loop was directed anteriorly, downward initially, and then up. In the frontal plane the loop was directed counterclockwise, pointing downward and to the left initially and upward and to the right terminally; most of the loop was located on the left.

The patient was considered to have levocardia with incomplete abdominal situs inversus. The cardiac findings were interpreted as being suggestive of ventricular septal defect, although the area of maximal intensity of the murmur was unusual.

The right side of the heart was catheterized. The catheter was introduced through a left cubital vein and advanced by way of the innominate vein and right superior vena cava into the right atrium. No left superior vena cava was encountered. The catheter was first passed from the right atrium into a hepatic vein (the impression on fluoroscopy was that this vein was entered directly from the right atrium and not by way of the inferior vena cava), withdrawn, and then advanced into the right ventricle and through a ventricular septal defect into the left ventricle. The latter was identified by fluoroscopy, pressure tracing, and oxygen saturation. The catheter was returned to the right ventricle and advanced into the left and right main pulmonary arteries. A wedge position was obtained in the right lung field. Measurements of pressure and the result of the determination of oxygen saturation are recorded in Table II.

The catheterization findings verified the presence of a ventricular septal defect, the right atrium as the true venous atrium, and the left atrium as the true arterial atrium.

Patient's kinship. The patient is the third of 8 children (6 sisters and 1 brother), all of whom are in good health. There was no parental consanguinity.

The patient's father is a slender man with kyphoscoliosis. He is long legged and has long feet. His body measurements are presented in Table I. His vision is good and there is no gross ocular defect, but ophthalmologic examination has not been made.

Table I. Body measurements

	Height	*Upper segment*	*Lower segment*	*Upper segment/ lower segment*	*Hand length*	*Foot length*	*Hand/ height ratio*	*Foot/ height ratio*	*Span*
Patient	1 54	6	78	0 97	18	24	11 7	15 6	155
Father	1 68	81	87	0 93	18	26 5	10 7	15 8	170 2
Normal				>0 93			<11	<15	

Table II. Catheterization findings

Position of catheter	*Oxygen saturation (%)*	*Pressure (mm. Hg)*
Superior vena cava	74	
Right atrium	74	a = 7 (mean 5) c = 1.5 v = 3.5
Right ventricle	81.5	38/0
Left ventricle	98	100/0
Pulmonary artery, main	84.5	37/7.5 (mean = 25)
Pulmonary artery, left	77	30/7 (mean = 16)
Pulmonary artery, right	82	37/7
Pulmonary capillary	99	7 (mean)

No evidences of cardiac abnormality were detected by physical examination, fluoroscopy, and electrocardiogram. He had had 13 brothers and sisters, but 12 died when they were very young, and no additional details about them could be ascertained. His only living sister is well at the age of 63.

The patient's mother, a woman of pyknic build, has 7 brothers and sisters, all of whom are living and well.

Discussion

When the abdominal viscera are transposed and the heart is on the left, the latter is nearly always abnormal. The cardiac anomalies are usually of such complexity that the exact diagnosis can be made only at postmortem examination. Campbell[2] divided the cases of levocardia with abdominal transposition into two groups. In the first group the superior vena cava and the venous atrium follow transposition of the abdominal organs and are on the left. In the second group the superior vena cava and venous atrium are in their normal position on the right side; a ventricular septal defect is almost always present.

Our patient belongs to Campbell's second group. He had no cardiac complaints whatsoever, and his cardiac anomaly was a purely incidental discovery. An interventricular septal defect was proved by





Fig. 2. Bronchograms which show the abnormal distribution of the bronchi of the right lung (*left*). The similarity of the distribution to that of the left lung (*right*) is apparent (the photograph of the left lung has been reversed purposely). This most probably indicates the presence of symmetrical bilobed lungs.



Fig. 3. Intravenous cholangiogram, showing the gall bladder located on the left side. The cardiac apex is also visible on the left.

cardiac catheterization and the vectorcardiographic pattern has been described as being characteristic of combined right and left ventricular hypertrophy *in the presence of an interventricular septal defect.*[1,6] Furthermore, direct drainage of hepatic veins into the right atrium is suspected. This form of anomalous hepatic venous drainage is a frequent finding in cases of levocardia.[3,11,21] It has been suggested that the abnormal hepatic veins represent persistent omphalomesenteric veins.[2]

Bronchography revealed an anomaly of the right bronchial tree suggestive of the presence of symmetrical bilobed lungs. In levocardia, anomalous lobation of the lungs seems to be the rule; the most frequent anomaly is symmetrical trilobed lungs.[3,13] In the literature we found only one instance of symmetrical bilobed lungs in levocardia.[15]

The occurrence of the many and apparently unrelated anomalies associated with levocardia may be better understood when the timetable of embryologic events is considered. The separation of the cono-truncus, the division of the atrioventricular canal, the initiation of pulmonary lobation, and the formation of the mesentery of the primitive gut all take place approximately between the thirty-first and thirty-sixth days of fetal life.[8] In this context it is *of interest that the spleen as well is laid* down in its primordial form during the

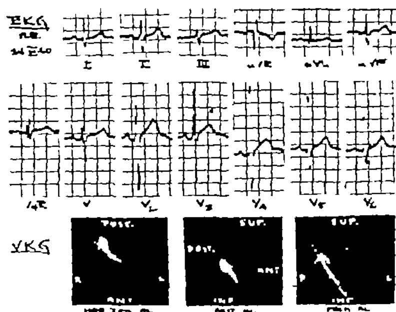


Fig. 4. Electrocardiogram shows incomplete right bundle branch block with rsR'S' pattern in Lead V_1, indicating early hypertrophy of the right side of the heart. The vectorcardiogram (pauses of 0.0025 second) verifies this in the horizontal plane tracing; however, the counterclockwise loop in the frontal plane indicates that left ventricular hypertrophy is present as well.

same period and that partial situs inversus is commonly associated with congenital asplenia.[15] In our case we were unable to prove either the presence or absence of the spleen.

The etiology of levocardia and other forms of malrotation of viscera is unknown. The causative factors are believed to be genetically controlled,[3,4,13] although there is no agreement as to the exact mode of transmission. Malrotation is thought to be inherited as a simple recessive trait[13] or it may be the result of more than a single recessive gene.[3]

Musculoskeletal defects occur frequently in many congenital malformations of the heart including malrotations. Keith[9] reported kyphoscoliosis and pectus carinatus in dextrocardia and Forgersen noted underdevelopment of the mandible in the same condition (quoted by Keith[9]). Hemivertebra and spina bifida have been described in cases of levocardia.[9,15]

In our patient a large span, kyphoscoliosis, pectus excavatum, high-arched palate, and underdevelopment of the mandible were present. This combination of skeletal changes is suggestive of Marfan's syndrome although prognathism is more common in the latter. Although the upper segment to lower segment ratio was within normal range, the hand height and foot height ratios were both distinctly high and compatible with the skeletal features of patients with Marfan's syndrome. That the patient's father, with an upper segment to lower segment ratio of 0.93 and foot height ratio of 15.8 (normal is below 15) may be considered to be of "border line" Marfan habitus, and that the patient's mother is a pyknic individual are pertinent observations. McKusick[10] emphasized the importance of Marfan features in relatives in confirming the diagnosis of this syndrome and stated that the marriage of a Marfan individual and a pyknic partner tends to normalize the skeletal habitus of their offspring.

Summary

The purely incidental discovery of an asymptomatic levocardia with ventricular septal defect and partial situs inversus is reported.

The possible relationship of the skeletal changes observed in this case and the Marfan syndrome are discussed.

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REFERENCES

1. Beregovich, J., Bleifer, S., Donoso, E., and Grishman, A. The vectorcardiogram and electrocardiogram in ventricular septal defect, with special reference to the diagnosis of combined ventricular hypertrophy. Brit. Heart J. 22:205, 1960.
2. Campbell, M., and Forgacs, P. Laevocardia with transposition of the abdominal viscera, Brit. Heart J. 15:401, 1953.
3. Campbell, M., and MacCarthy, D. Morbus coeruleus with inversion of the abdominal viscera in two cousins, Guy's Hosp. Rep. 106:18, 1957.
4. Campbell, M. The genetics of congenital heart disease and situs inversus in sibs, Brit. Heart J. 21:65, 1959.
5. Campbell, M. Laevocardia with transposition of the abdominal viscera. Case report, Brit. Heart J. 22:432, 1960.
6. Dack, S. The electrocardiogram and vectorcardiogram in ventricular septal defect, Am. J. Cardiol. 5:199, 1960.
7. Fitzgerald, M. J. F. Isolated laevocardia with situs inversus viscerum. Case report, Brit. Heart J. 22:129, 1960.
8. Ivemark, B. Implications of agenesis of the spleen on the pathogenesis of cono-truncus anomalies in childhood, Acta paediat. 44:590, 1955, and Supplement 104.
9. Keith, J. D., Rowe, R. D., and Vlad, P. Heart disease in infancy and childhood, New York, 1958, The Macmillan Company.
10. McKusick, V. A. Heritable disorders of connective tissue, St. Louis, 1960, The C. V. Mosby Company.
11. Moscovitz, H. L., Gordon, A. J., and Scherlis, L. Levocardia, Am. Heart J. 44:184, 1952.
12. Nadas, A. Pediatric cardiology, Philadelphia, 1957, W. B. Saunders Company.
13. Overholt, E. L., and Bauman, D. F. Variants of Kartagener's syndrome in the same family, Ann. Int. Med. 48:574, 1958.
14. Portillo, B., Anselmi, G., Sodi-Pallares, D., and Medrano, G. A. Importance of the unipolar leads in the diagnosis of dextrocardias, levocardias, dextropositions, and dextrorotations, Am. Heart J. 57:396, 1959.
15. Putschar, W. G. J., and Manion, W. C. Congenital absence of spleen and associated anomalies, Am. J. Clin. Path. 26:429, 1956.

Myotonic dystrophy with electrocardiographic abnormalities Report of a case

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Myotonic dystrophy (myotonia atrophica Steinert s disease) is a familial disease characterized by myotonia and progressive atrophy of selected muscle groups Extramuscular degenerative changes are reflected in the development of cataracts premature frontal baldness testicular atrophy and cardiac disease Evidence of cardiac disease in the pa with myotonic dystrophy is found st commonly in the electrocardiogram. DeWind and Jones[1] noted a 60 per cent incidence of electrocardiographic abnormalities in a review of 98 cases of myotonic dystrophy with electrocardiographic stud ies recorded Fisch[2] reported a 68 per cent incidence of electrocardiographic abnor malities in his review of 85 cases The abnormal changes most frequently seen were a prolonged P R interval low P waves and delayed intraventricular conduction.

In the following report of a case of myotonic dystrophy the electrocardiogram recorded at rest revealed a prolonged P R interval and low to flat P waves, and an electrocardiogram recorded after maximum exercise showed the pattern of complete left bundle branch block.

Case report

This 43-year-old white male Air Force pilot first observed symptoms of myotonia in 1956. He noted difficulty in relaxing the jaws during the initial moments of mastication and experienced mild spasm of the tongue during the first few moments of speech. In 1958, he observed a transient inability to relax his grip Either fatigue or cold would intensify the myotonia. On evaluation in July 1961 the patient denied any increase in the severity of the myotonia.

In 1957 he noticed that he required a collar one-half size smaller than formerly This was explained when a physician discovered bilateral atrophy of the sternocleidomastoid muscles.

Frontal baldness commenced during his twenties and had gradually increased over the years. A number of the patient s uncles were bald but premature baldness was not a family trait

The patient and his wife had been unsuccessful in having children, although his sperm had been studied and had been reported to be normal There was no family history of testicular atrophy or sterility

Ophthalmologic examination in January 1961 had revealed opacities of the lenses typical of those seen in myotonic dystrophy The opacities of the lenses had not interfered with his visual acuity There was a history of senile cataracts on both sides of his family

Serial electrocardiograms from 1956 through 1960 showed low P waves and P R intervals of 0.19 to 0 20 second

There was no family history of any symptomatology which suggested myotonia or muscular dystrophy

Physical examination revealed a well-developed and well-nourished white man who was 43 years of age, 69 inches in height, and weighed 160 pounds. The blood pressure was 130/75 mm. Hg and the pulse 80. The patient had a high forehead with prominent frontal bosses and a somewhat long and narrow face.

Significant ophthalmologic findings were limited to the lenses. The slit-lamp examination revealed a zone of clear cortex adjacent to the capsule Central to this zone was a concentration of cortical punctate and iridescent crystalline opacities, mainly aggregated in the posterior cortex. Pos-

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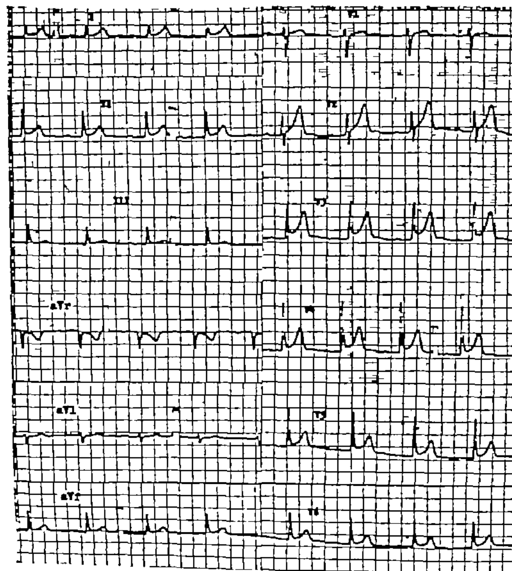


Fig. 1. Electrocardiogram recorded with patient in basal state. Low to flat P waves. P-R interval of 0.24 second.

teriorly the cortical sutures were marked by increased relucency resulting in a "rosette." Some small water clefts and very early lamellary separation in the anterior cortex were seen. All of these changes were bilateral.

The heart was not enlarged. The heart sounds appeared to be unusually distant for a patient with a thin chest wall. A Grade 1 systolic murmur that disappeared in some phases of respiration and varied in intensity with respiration was heard over the left anterior precordium. The cardiac rhythm was regular.

Bilateral weakness of the frontalis muscle was noted. Slight weakness of the other facial muscles and the orbicularis oculi was present. A fairly marked myotonic response of the masseter and temporalis muscles could be detected with the first contraction, but was not present on subsequent contractions. When the tongue was struck by a percussion hammer a "worm-like" contraction was observed. A minimal myotonic response of the thenar muscles was evoked. Marked atrophy and weakness of both sternocleidomastoid muscles were apparent.

The testicles appeared to be normal in size. The remainder of the physical examination gave findings within normal limits.

Complete blood count, urinalysis, VDRL, serum alkaline phosphatase, blood urea nitrogen, serum sodium, serum potassium, serum chloride, serum calcium, serum phosphorus, serum bilirubin, thymol turbidity, cephalin flocculation, SGOT, SGPT, total protein and A-G ratio, protein-bound iodine, serum creatinine, serum cholesterol, serum phospholipids, and a glucose tolerance test were all within normal

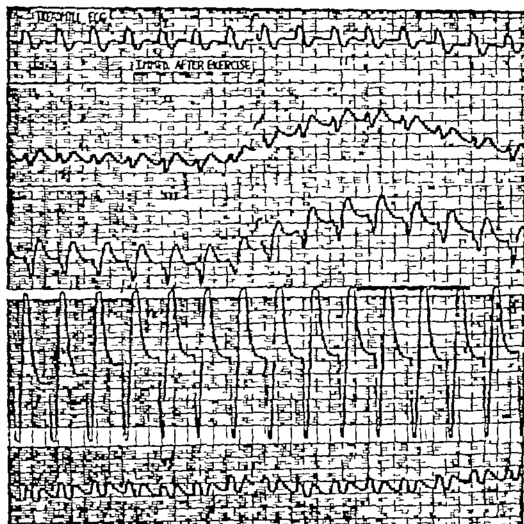


Fig. 2. Treadmill postexercise electrocardiogram. Complete left bundle branch block.

limits. A chest x-ray film was normal. Measurements of 24-hour urinary creatinine, creatine, and 17-ketosteroid levels performed at another hospital in February 1960, were within normal limits. Electromyography had demonstrated the typical action potentials of myotonia.

Routine electrocardiograms which were recorded when the patient was in the fasting, resting state revealed low to flat P waves and prolongation of the P-R interval to 0.24 second (Fig. 1). A double Master's exercise test revealed no significant electrocardiographic changes; the maximum heart rate recorded in the postexercise tracings was 90. An electrocardiogram recorded after the patient had exercised for 13 minutes on the treadmill showed a complete left bundle branch block at a cardiac rate of 120 (Fig. 2). (The pulse had risen to a rate of 168 just before the treadmill was stopped.) With a cardiac rate of 90, complete left bundle branch block was still present on a tracing recorded 8 minutes after exercise. The electrocardiogram recorded on the following day revealed a return to normal intraventricular conduction.

Comments

When present, abnormal cardiovascular physical findings in the patient with myotonic dystrophy are usually minor and nonspecific, consisting of such meager findings as hypotension, poor heart tones, splitting of the first heart sounds, and soft systolic apical murmurs.[1,2] In our patient the distant heart tones and unimpressive systolic murmur conformed to this nonspecific pattern. An occasional patient will develop cardiac enlargement or congestive heart failure or both.

Death due to myotonic dystrophy heart disease has resulted from acute heart failure and from ventricular tachycardia secondary to complete heart block.[3-6] In a postmortem examination of a patient who died in acute heart failure, Spillane[4]

found no cardiac pathology other than ventricular dilatation. On the other hand in the examination of the heart of a patient with atrial flutter who also died in acute heart failure, Fisch and Evans[3] described striking microscopic pathology which consisted of diffuse fibrosis with separation of muscle fibers by fibrous connective tissue and scattered hypertrophied muscle fibers with large rectangular nuclei.

Although first-degree heart block, low P waves, and prolonged intraventricular conduction time are the most common electrocardiographic abnormalities, other conduction defects (second-degree A-V block, complete A-V block, and complete left bundle branch block) and atrial arrhythmias (atrial flutter and atrial fibrillation) have been described.[1-4] Kuhn[6] reported a case of myotonic dystrophy in which serial electrocardiograms over a 10-year period demonstrated progressive changes from normal ventricular conduction to intermittent complete left bundle branch block to permanent complete left bundle branch block; a prolonged P-R interval, which had preceded the development of the bundle branch block, was noted in all tracings.

In this patient the electrocardiographic abnormalities would appear to be sufficiently distinctive in the presence of known myotonic dystrophy to allow the diagnosis of cardiac involvement by the disease. In a patient 43 years of age, one must consider the possibility of coronary artery disease as the etiology of the electrocardiographic abnormalities. On the basis of an almost equal incidence of abnormal electrocardiograms in patients under and over the age of 45, DeWind and Jones[1] concluded that the electrocardiographic abnormalities reported in patients with known myotonic dystrophy could not be ascribed to coronary disease.

The development of a complete left bundle branch block after the patient had exercised on the treadmill deserves further comment. Shearn and Rytand[7] emphasize that in most cases, intermittent bundle branch block eventually becomes permanent. Studies from this laboratory indicate that complete left bundle branch block, intermittent or permanent, indicates some type of cardiac disease. In contradistinction to right bundle branch block, left bundle branch block probably has not occurred as an isolated congenital finding. In a study of 122,043 subjects, only 17 examples of complete left bundle branch block were found.[8] In the majority of the subjects a past history suggestive of an acquired defect of the heart was obtained. In over 44,000 individuals who were under the age of 25, no single instance of complete left bundle branch block was discovered.

Summary

A case of myotonic dystrophy is presented with the electrocardiographic findings of low to flat P waves, the serial development of first-degree heart block, and the appearance of complete left bundle branch block after maximal exercise.

REFERENCES

1. DeWind, L. T., and Jones, R. J.: Cardiovascular observations in dystrophia myotonica, J.A.M.A. 144:299, 1950.
2. Fisch, C.: The heart in dystrophia myotonica, Am. Heart J. 41:525, 1951.
3. Fisch, C., and Evans, P. V.: The heart in dystrophia myotonica: report of an autopsied case, New England J. Med. 251:527, 1954.
4. Spillane, J. D.: The heart in myotonia atrophica, Brit. Heart J. 13:343, 1951.
5. Litchfield, J. A.: A-V dissociation in dystrophia myotonica, Brit. Heart J. 15:357, 1953.
6. Kuhn, Von E.: Entwicklung eines Linksschenkelblocks bei myotonischer Dystrophie, Schweiz. med. Wchnschr. 90:1160, 1960.
7. Shearn, M. A., and Rytand, D. A.: Intermittent bundle branch block, A.M.A. Arch. Int. Med. 91:448, 1953.
8. Hiss, R. G., and Lamb, L. E.: Electrocardiographic findings in 122,043 individuals, Am. J. Cardiol. (In press)

Congenital aneurysms of sinus of Valsalva
A clinical study

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The prognosis of congenital aneurysms of the sinus of Valsalva is very poor the majority of patients die of congestive failure within 1 year after rupture of the aneurysm This most distressing cardiac lesion which proved to be universally fatal up until 5 years ago has become amenable to surgical treatment in recent because of the rapid advance in pen-heart operation.

The successful cure of this abnormality is one of the most striking contributions of cardiac surgery Up to the present time the extreme difficulty in diagnosing this heart disease has prevented any detailed discussion of this problem. During the treatment of numerous patients at our Heart Institute however we have found that the diagnosis of this malformation is not at all so difficult as it seemed. The diagnosis can be established with considerable accuracy by means of careful routine clinical examinations when the anatomic classification[1] previously reported is fully understood and when the direction of the jet of blood gushing out through the rupture is visualized mentally The clinical symptoms have been arranged according to the types of aneurysms so as to facilitate the diagnosis, in the hope that these patients would be discovered early and saved by surgical intervention

Age and sex

In general aneurysms of the sinus of Valsalva of Types I II IIIv IIIa and IV produce no symptoms and in most instances, are not discovered until rupture occurs. The ages of the patients when rupture occurred were as follows Type I—ages 13 to 41 years average 29 Type II—age 30 years Types IIIv and IIIa—ages 11 to 56 years average 33 and Type IV—ages 22 to 67 years average 34

Rupture appeared to occur most frequently at about the age of 32 years. Fowler's case of aneurysmal rupture in a 4-year-old patient[illegible] was not confirmed by autopsy

The Type Ivsd aneurysm is discovered quite early because symptoms of interventricular septal defect and aortic insufficiency are manifested soon after birth and because most of the patients are kept under supervision. In our series of cases a cure was successfully effected by operation in Case 7 (at age 10 years) and in Case 11 (at age 5 years)

Of the 50 cases in which the type of lesion was definitely established only 12 were female patients, which indicates the preponderance of male patients. The ratios for the various types of aneurysms are as follows Types I and Ivsd—male to female ratio 15:6 (60-40 per cent) Types IIIv

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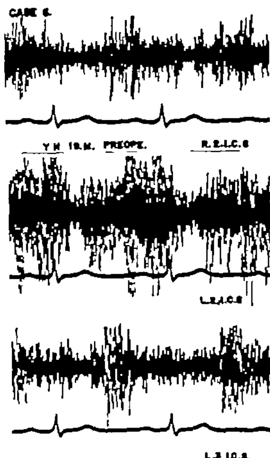


Fig. 1 Phonocardiogram of ruptured Type I aneurysm. Case 6, 19-year-old boy

and IIIa—male to female ratio 9.3 (67.33 per cent) Type IV—male to female ratio 9.2 (72.22 per cent)

It is difficult to suppose that during the embryologic development of the sinus of Valsalva a difference between the sexes exists in the formation of fragile areas. Most likely the cause of this wide difference in the incidence between males and females is through some factor which is present after birth and which acts on the weak area to produce the aneurysm The chief role might be the difference in the load demand of the heart between the two sexes

Subjective symptoms

Type I The 4 cases of Type I aneurysm which we encountered were all seen after rupture had occurred In Cases 1 2, and 6 the heart murmurs were detected prior to rupture. The cause of the systolic murmurs in these patients was probably due to infundibular stenosis caused by projection of the aneurysm into the outflow tract of the right ventricle. The time of rupture in Case 6 as well as in Case 2 of Jones and Langley was quite definitely established The former patient, after running about 100 meters to catch a bus, suddenly experienced stabbing pain in the left chest, which extended to the back. The pain lessened after he had sat quietly in the bus for about 5 minutes, but shortness of breath palpitation and constriction of the chest became intense. Still the patient felt well enough to go to a movie and walk home. The next day signs of cardiac insufficiency oliguria and edema set in. This state of cardiac insufficiency continued for about 1 year after which time he was completely cured by operation. The other patient (Case 2) of Jones and Langley lived for 17 years after rupture had occurred during which period he experienced symptoms of congestive failure from time to time. The time of rupture of the aneurysms in Cases 1 and 2 of our series was not definitely established but the patients survived for 4 and 7 years, respectively after onset of symptoms. These cases indicate that rupture of the Type I aneurysm of the sinus of Valsalva does not pursue an abrupt course.

Type Ivsp Rupture of a Type Ivsp aneurysm is not associated with an acute attack During a period of about 1 year there is insidious onset of palpitation shortness of breath, compression of the chest chest pains, and edema, which lead eventually to heart failure. Therefore, the period from rupture to death is not definite. In many cases the patient comes for examination not because of any subjective symptoms, but for a physical checkup because distinct heart murmurs had been detected by a doctor Of the 15 patients in whom the clinical symptoms have been described 3 were completely without any symptoms, and the other 12 had heart failure after gradual onset of palpitation shortness of breath and compressed feeling in the chest.

Type II In Case 12 of our series the patient experienced acute constriction of the chest and difficulty in breathing while

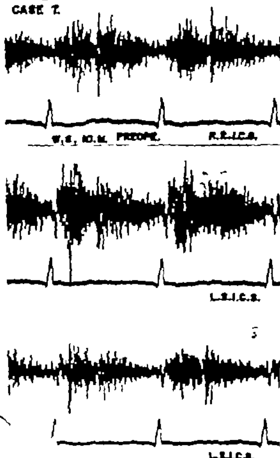


Fig. 2. Phonocardiogram of Type IIIv aneurysm. Case 7. 10-year-old boy.

sleeping. Breathing became easier after several hours, and by the next day only mild palpitation remained. The patient was operated on 2 years later and two episodes of endocarditis occurred before complete cure was attained.

Type IIIv. Because cases are few in number the symptoms in each case will be described. The patient reported on by W. G. Bigelow[3] was an apparently healthy man who suddenly experienced acute pain in the right upper abdomen while he was watching a movie. This attack of pain subsided spontaneously after 10 minutes and was followed by gradual onset of constriction of the chest. The next day he experienced shortness of breath and pain in the right upper quadrant when he exerted himself. Lillehei's[4] Case 1 was an 11-year-old girl who developed normally until she was 7 months old, but after that age her growth was retarded, her general condition suddenly began to deteriorate, and she was prone to catch cold easily. This period probably coincided with the time of rupture. Lillehei's second patient[4] suddenly complained of tachycardia and angina-like pains. On the next day symptoms of heart failure with engorgement of veins, râles in both lung fields, and enlargement of the liver set in. In either case it appeared that the opening made by the rupture was fairly large and that through it a large amount of blood passed into the right ventricle during systole, resulting in resistance against the normal stream of blood from the right atrium through the tricuspid valve into the right ventricle, which thus produced increased venous pressure. The right upper abdominal pain described in the report is thought to have been due to sudden congestion of the liver.

Type IIIa. The case of a Type IIIa aneurysm reported by Venning[7] began with progressive edema and was complicated by signs of tricuspid insufficiency. But this case is an exception since all the other cases showed abrupt onset at rupture with acute pain in the upper abdomen and vomiting suggestive of some disorder of the gastrointestinal tract, followed after a while by manifestation of symptoms referable to the heart such as chest pain, dyspnea, and palpitation. A typical case is that reported by Macleod[8] of a 54-year-old man who was in the best of health until 2 weeks prior to hospitalization when he suddenly experienced abdominal pain, emesis, and shortness of breath. The abdominal pain and vomiting subsided in 1 hour but was followed by reduced exercise tolerance. The slightest exercise caused shortness of breath and palpitation whereas more strenuous exertion produced severe radiating pain from the sternum down to the right arm. Edema of the ankles was first noted 1 week prior to admission. From this time he began to cough and was awakened at night by paroxysmal attacks of dyspnea. Mercurial diuretics and digitalis preparations were of no avail, the condition of congestive failure progressed, and the patient expired 1 week after being admitted to the hospital.

In general, death from cardiac insuf-

ficiency ensues in about 4 weeks after the occurrence of the rupture. No definite pattern in respect to the time of rupture was found some ruptures occurred while the patient was asleep whereas others occurred when he was seated before a desk. An interesting case was that of a man who died almost immediately after falling from an apartment building and who was later found at autopsy to have a rupture of a Type IIIa aneurysm of the sinus of Valsalva.[7] Another patient appeared to have had rupture of the aneurysm from the shock of an automobile accident which presents an interesting problem from the standpoint of forensic medicine.

Type IV All the cases of Type IV aneurysm show prominent symptoms at the time of rupture. Severe chest pain or upper abdominal pain and emesis occur within a short period These symptoms are partially relieved after a few minutes but are followed by increasing difficulty in breathing and palpitation About 3 to 4 weeks later the patient dies of progressive congestive failure

A rare case which we observed was that of a patient who lived a normal life for 8 years after rupture had occurred (Case 10) This 28-year-old married woman reported that while climbing up a mountain in 1952 she suddenly felt pain in her upper abdomen this pain eventually extended to the area of her heart when she inhaled the smell of sulphur fumes. She gained some relief from the pain after squatting for a while, but palpitation became severe and she had difficulty in breathing when she started to walk on. An episode of vomiting occurred while she was climbing down the mountain and she was immediately taken to a hospital where her condition was diagnosed as cholecystitis. Palpitation and dyspnea gradually improved after 20 days of hospital care, and she was able to return to daily activities. In June 1957 she was treated in a hospital for about 4 months for endocarditis. She married in 1958 and that winter shortness of breath became intense and she was bothered by persistent cough and expectoration The following year discharge of sputum subsided but difficulty in breathing persisted. In 1960 she experienced some shortness of breath but was able to perform her household work. She was admitted to our hospital in this condition and underwent an operation with eventual cure. In contrast to the long clinical course in this patient another case has been reported[8] in which the patient died within a few seconds after rupture.

At the time of rupture the activities of the patients varied from talking on the telephone sawing wood hiking to sleeping etc. and no definite pattern in the circumstances precipitating the rupture could be found

From the foregoing description of our cases and those found in the literature it is possible to form a general picture of the symptomatology of ruptured aneurysms of the sinus of Valsalva. (*1*) *Time of rupture* Sudden onset of angina like pain or right upper abdominal pain associated with nausea and emesis persisting for about 1 hour (*2*) *Intermittent period* Alleviation of the severe symptoms of rupture with subsequent onset of exertional dyspnea and constriction of the chest, which persist for about 24 hours. (*3*) *Period of congestive failure* Manifestation of cough, edema oliguria and other signs of cardiac insufficiency leading to death after several months.

In Types I and IVsb the aneurysm protrudes into the conus and produces infundibular stenosis, or because of the preexisting ventricular septal defect the circulatory forces are altered and the cardiopulmonary functions as a whole are changed to adapt to the abnormal forces. Therefore the production of an aorticocardiac fistula and the subsequent alteration of the circulation does not produce such a severe shock thus accounting for the absence of typical symptoms of rupture in these cases. In contrast when an aortico-cardiac fistula is suddenly produced in ruptures of Types II III and IV aneurysms where normal circulatory forces were present, the effect on the cardiopulmonary functions is great and leads to the onset of severe symptoms at the time of rupture

Heart murmurs and thrills

Type I A very loud murmur of the to-and fro type is audible in greatest intensity

at the orifice of the pulmonary valve. By auscultation it is impossible to distinguish the type of murmur because of its great loudness, but with the cardiograph both the systolic and diastolic murmurs show different peaks of intensity with greatest accentuation of the diastolic murmur. Fig. 1 shows the cardiogram taken after rupture of a Type I aneurysm of the sinus of Valsalva. A thrill is elicited over the orifice of the pulmonary valve during both the systolic and diastolic phases, but more strongly during diastole. Before rupture has occurred a systolic murmur is audible at the orifice of the pulmonary valve resembling that of pulmonary stenosis.

Type Ivsd. Without exception heart murmurs are detected soon after birth, but this murmur is caused by high intraventricular septal defect and is heard loudly and clearly. When there is progressive insufficiency of the aortic valve, a diastolic blowing murmur is audible at the level of the third intercostal space over the sternum at the midline. The systolic and diastolic murmurs overlap and can be heard as a continuous sound along the left border of the sternum. These murmurs resemble those associated with patent ductus arteriosus, and thoracotomy has been performed because of a mistaken diagnosis.[9,19] Although the auscultatory finding is confusing, cardiograms show that the murmur of the Type Ivsd aneurysm of the sinus of Valsalva is of the to-and-fro type, with two distinct peaks of intensity which correspond to the systolic and diastolic phases, thus distinguishing it from the murmur produced by a patent ductus, since the latter shows a continuous murmur from the systolic to the diastolic period with the peak at the second sound. Fig. 2 shows the cardiogram taken from a patient with an intact aneurysm of Type Ivsd.

Type II. No murmurs are audible prior to rupture of the aneurysm. The murmur produced after rupture is similar to that heard after rupture of a Type I aneurysm but is best heard slightly more to the right.

Type IIIv. Bigelow reported that in his first case the murmur was heard best at the left border of the sternum between the fourth and fifth ribs. The murmur was continuous, but a thrill was not reported.



Fig. 3. *A*, Right anterior oblique projection. *B*, Posteroanterior projection. *C*, Left anterior oblique projection.

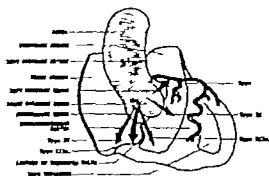


Fig. 4. Schematic representation of the frontal roentgenogram of the heart (Fig. 3,B).

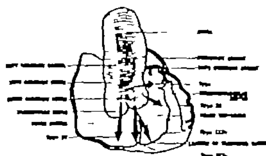


Fig. 5. Schematic representation of the right anterior oblique roentgenogram (Fig. 3,A).

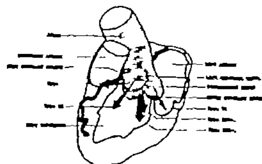


Fig. 6. Schematic representation of the left anterior oblique roentgenogram (Fig. 3,C).

In both of Lillehei's cases, the loudest point of the continuous murmur was found between the right third and fourth ribs at the border of the sternum. A systolic thrill was also present.

Type IIIa. A loud continuous murmur is audible from the lower end of the sternum to the upper abdomen. The murmur is strongest during systole and in most instances the thrill is felt only during systole.

Type IV. The type and point of greatest intensity of the murmur is identical with that of Type IIIa but the sound is much weaker and a thrill is not present in most instances. In our Case 10 there was a continuous murmur which was heard best during systole in the fifth intercostal space from the border of the sternum to the mid-line and which was audible over a wide area from the upper abdomen to the right side of the chest. The sound was weaker than that heard in Types I and II, softer and more distant. Naturally, a thrill was not obtained but during operation a localized systolic thrill was felt behind the right atrium near the sulcus terminalis.

The foregoing description of the character of the various murmurs and their location can be explained by the direction of projection of the aneurysms, and when rupture occurs by the direction of the jet stream which bursts from the opening made by the rupture. To clarify this relationship metal arrow markers were placed in a normal heart pointing in the directions that would be taken by the blood gushing through the holes made by the rupture of the various types of aneurysms and x-ray films were taken from three directions. The x-ray films were taken after barium was applied to the walls of the sinus of Valsalva (Figs. 3, 4, 5, and 6). The auscultatory findings could be assessed with considerable accuracy when this picture was visualized.

Roentgenographic findings

By chance, an x-ray film of the chest in Case 1 was taken just prior to rupture of the aneurysm and comparison with the film taken after rupture was possible (Fig. 7). Bilateral dilatation of the cardiac shadow and intensification of pulmonary markings was striking. With sudden influx of a large amount of blood to the normal pulmonary circulation, the pulmonary markings were intensified and pulsation of the peripheral vessels was noted. Fig. 8 shows the chest x-ray film of a patient 8 years after rupture of a Type IV aneurysm. The enlargement of the right atrium is noted. When retrograde aortography



Fig. 7. Frontal roentgenograms of the chest taken just prior to rupture (*top*) of a Type I aneurysm of the sinus of Valsalva and after rupture (*bottom*). Case 1.

shows the presence of an aneurysm a definite diagnosis can be given but generally the poor condition of these patients does not permit the forceful injection of thick contrast material into the root of the aorta. Falholt[13] has succeeded in obtaining a clear picture of an intact aneurysm of the sinus of Valsalva. Recently Morrow[13] presented a film which showed a ruptured Type IIIa aneurysm and the jet stream which resulted from it. A clear picture of the anatomy of the aneurysmal formation can be grasped with retrograde aortography together with the descriptions given in Figs. 3 and 6 and in the planning of surgical treatment should prove of valuable assistance. Therefore whenever circumstances permit this procedure should be attempted.

Electrocardiographic findings

No distinctive electrocardiographic features are presented by aneurysms of Types I and Ivsd. In all of the cases the electrocardiograms showed sinus rhythm and either left ventricular hypertrophy or bilateral hypertrophy with left ventricular preponderance. Figs. 9 and 10 show the electrocardiograms of Types I and Ivsd aneurysms, respectively.

The electrocardiograms of Types IIIa IIIv and IV aneurysms show left ventricular hypertrophy with left ventricular preponderance in addition to diastolic overload of the right ventricle. In Case 10 of our series the electrocardiogram showed incomplete right bundle branch block (Fig. 11). The distinctive findings in Types III and IV are A-V block,[4,14] prolongation of P-Q,[4,14] A-V nodal rhythm,[15] right bundle branch block,[4,4] and Wenckebach cycle,[14] showing predominantly impairment of the conduction system. A case has been reported[14] of a patient who died when complete A-V block developed im-



Fig. 8. Chest x-ray film taken 8 years after rupture of a Type IV aneurysm. Case 10, 28-year-old woman.

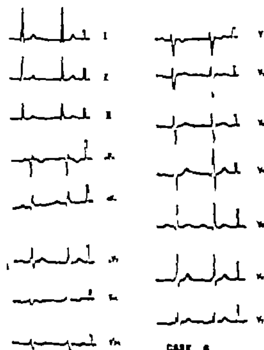


Fig. 9 Electrocardiogram of Type I aneurysm from a 19-year-old boy

mediately after the opening made by the rupture was closed at operation, and caution in this regard is required. Because the site of the Types III and IV aneurysms projects toward the atrial node the bundle of His, and to the area through which the right branch of the conduction system courses, these distinctive electrocardiographic features agree with the anatomic relationship.

Hemodynamics

Type I After rupture occurs, oxygenation of the blood in the outflow tract of the right ventricle is increased A continuous pressure curve traced when the cardiac catheter is slowly withdrawn from the pulmonary artery to the right ventricle shows a pattern suggestive of infundibular stenosis.

Type IVsp The interpretation of the results of cardiac catheterization is difficult in this type because a high interventricular septal defect exists. In Fig 12,*A* the opening of the interventricular septal defect is big which results in a marked increase in the oxygenation of the blood in the right ventricle. When an aneurysm bulges into the interventricular septal defect and closes the shunt as shown in Fig 12,*B* the increased oxygen tension in the right ventricle is on the contrary reduced On the other hand the projection of the aneurysm into the outflow tract of the right ventricle produces infundibular stenosis, and the pressure curve which is traced when the catheter is withdrawn through this area presents a picture of infundibular stenosis (Fig 13) This phenomenon was present in Cases 7 and 8 in our series and in the case reported by T K. Lin [11] The degree of projection of the aneurysm can be surmised to some extent by the degree of increase in the oxygen tension in the right ventricle, and by the degree of infundibular stenosis shown by cardiac catheterization studies.

Type II No abnormal pattern of the continuous curve obtained by withdrawal of the catheter from the pulmonary artery is found Of course the oxygen content of the right ventricle is elevated.

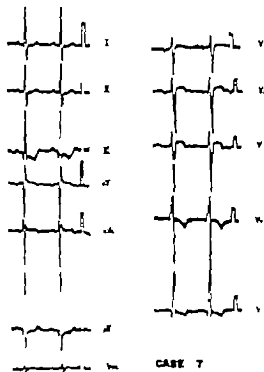


Fig. 10 Electrocardiogram of Type IVsp aneurysm from a 10-year-old boy

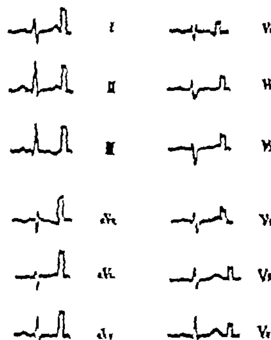


Fig. 11. Electrocardiogram of Type IV aneurysm from a 28-year-old woman.

Type IIIc. Discussion of this type is necessarily brief since we have not personally observed any cases. It is obvious, however, that the oxygen tension of the blood in the inflow tract of the right ventricle would be increased. No findings which indicate infundibular stenosis are made.

Types IIIa and IV. Because both of these types present a similar pattern of circulatory forces they will be discussed together. The oxygenation of the blood in the atrium is raised, and, as when an atrial septal defect exists, the blood oxygen tension in the right ventricle is increased in many cases. When the flow of blood through the shunt is excessive, the right atrial pressure is elevated, with increased amplitude of the v wave.

Diagnosis

The dye-dilution technique used to diagnose rupture of an aneurysm of the sinus of Valsalva[1,47] is not considered to be an important diagnostic method. When the anatomic relationship between the type of aneurysm which exists and the direction in which it is prone to rupture are accurately grasped, and when the descriptions given in Figs. 3-6 are kept in mind during careful examination of the patient, a considerably accurate diagnosis can be given. The history should be obtained in detail, and with routine clinical investigations, such as electrocardiography, chest x-ray film, and fluoroscopy, that can be performed in any hospital, the lesion can be satisfactorily diagnosed. When operation is contemplated, however, cardiac catheterization and retrograde aortography should be performed to obtain maximum results.

Prognosis

The outcome depends upon the type of aneurysm and the site of the rupture, and in these cases varied between immediate death and survival for 17 years after rupture, but in the majority of the cases death intervenes within 1 year because of progressive cardiac insufficiency. Endocarditis is frequently a complication which hastens the death of the patient. This lesion does not respond to medical management, so that surgical treatment should be considered as soon as these cases are discovered.

Differential diagnosis

1. Time of rupture. Rupture of the ventricular septum due to myocardial infarction produces symptoms similar to those of rupture of an aneurysm of the sinus of Valsalva.[15-21] The history of the patient as to previous signs of coronary insufficiency and hypertension aids to some extent in the differential diagnosis. However, the electrocardiograms and auscultatory examination must be relied upon for definite diagnosis. In the case of rupture of the ventricular septum, electrocardiographic evidence of fresh infarction is obtained. In addition, the cardiac murmur is systolic and heard best at the apex. Rupture of the papillary muscles due to myocardial infarction also gives signs which resemble the symptoms of rupture of an aneurysm, but there is evidence of infarction in the electrocardiograms, and the murmur heard is systolic, which makes it possible to differentiate the two.

2. Heart murmurs. Rupture of an aortic aneurysm into the pulmonary artery,[22] patent ductus arteriosus, aortic septal defect,[23,24] and anomalous coronary ar-

Aorta
Pulmonary artery
I2.0 Vol%
I7 2 Vol%
Pulmonary artery
Aorta
Right atrium
Aneurysm
V S.D
Left ventricle
I6 0 Vol%
Right ventricle
Interventricular septum
I2 8 Vol%
I2 4 Vol%
I2 9 Vol%
A
B

Fig. 12. Comparison of circulatory forces of Stage 1 of a Type I aneurysm with those of Stage 3.



Fig. 13. Pressure curve traced when the cardiac catheter was slowly withdrawn from the pulmonary artery to the right ventricle. Case 9, 8-year-old girl.

tery[illegible] each produce a continuous murmur similar to that heard after rupture of an aneurysm of the sinus of Valsalva. In patent ductus arteriosus the point of greatest intensity of the murmur is in the second left intercostal space with radiation to the subclavicular region. In addition no history pointing to rupture is obtainable. The point of greatest intensity of the murmur in aortic septal defect is almost the same as that in cases of aneurysms of Types I, IVSD and II. Determination of the site of the shunt may help in the differentiation of this lesion.

Differential diagnosis is difficult when aortic insufficiency is associated with a high interventricular defect. This difficulty is obvious when we consider that Type IVSD aneurysm is but a different gradation in the same disease process that produces a high interventricular septal defect with aortic insufficiency. It has already been mentioned that cardiac catheterization aids to some extent in distinguishing the gradations of this abnormality.

Operation

Types IIIa and IV. Surgical correction of these types of aneurysms under hypothermia[illegible] is possible but the combined use of the artificial heart lung is safer.[illegible] The lesion can be successfully repaired by closure of the aneurysm at its base with continuous or interrupted sutures.

Type IIIc. We have not had any experience with this type but Lillehei[4] and Bigelow[3] have obtained good results by suturing the base of the aneurysm using extracorporeal circulation and entering the heart through the right ventricle.

Type I. For this type the operative procedure followed in Case 6[1] of our series will be described. Using moderate hypothermia and the heart lung apparatus, we incised the right ventricle and root of the aorta, disclosing the origin of the aneurysm from the right coronary sinus. After the aneurysm had been excised, the defect was sutured and closed and care was taken not to injure the coronary artery. For good measure this area was reinforced with an Ivalon patch placed from the aortic to the right ventricular side. Adequate results have been obtained with this procedure but evaluation of this method will have to await additional investigation since this is the only case in which operation has been carried out.

Type IVSD. This type of aneurysm is very difficult to manage surgically. We have had a disagreeable experience with one case which ended fatally when rupture recurred postoperatively. Many failures have also been reported in the literature.[illegible] The surgical procedure is complicated by the fact that the upper border of the aneurysm is formed by a part of the fragile tissue of the sinus so that there is therefore no strong support for the sutures, and by the fact that the interventricular septal defect must also be closed when the aneurysm is excised. In addition complete correction of the deformed aortic valve cannot be hoped for. In our series of cases, those in which the lesions were of Stage 2 or less in severity were managed by insertion of the aneurysm into the left ventricle and closure of the ventricular septal defect, which improved the aortic insufficiency to some extent.

Type II. Procedures identical to those used to repair the Type I aneurysms are satisfactory for this type.

In conclusion the symptomatology has been arranged on the basis of our previously reported classification of congenital aneurysms of the sinus of Valsalva, in the hope that this presentation would facilitate the diagnosis of rupture of these aneurysms and thereby save the lives of as many patients as possible through early surgical management.

REFERENCES

1. Sakakibara, S., and Konno, S.: Congenital aneurysm of sinus of Valsalva. Anatomy and classification, Am. Heart J. 63:405, 1962.
2. Jones, A. M., and Langley, F. A.: Aortic sinus aneurysm, Brit. Heart J. 11:325, 1949.
3. Bigelow, W. G., and Barnes, W. T.: Ruptured aneurysm of aortic sinus, Ann. Surg. 150:117, 1959.
4. Lillehei, C. W., Stanley, P., and Varco, R. L.: Surgical treatment of ruptured aneurysm of the sinus of Valsalva, Ann. Surg. 146:459, 1957.
5. Venning, G. R.: Aneurysm of the sinus of Valsalva, Am. Heart J. 42:57, 1951.
6. Macleod, A.: Cardio-aortic fistula, Brit. Heart J. 6:194, 1944.
7. Hauser, H.: Aneurysma des Sinus Valsalvae mit Durchbruch in den rechten Vorhof, Deutsche Ztschr. ges. gerichtl. Med. 32:490, 1940.
8. Kawasaki, I. A., and Benenson, A. S.: Rupture of an aneurysm of a sinus of Valsalva into

the right auricle, Ann. Int. Med. 25 150 1946.
9 Morgan, E. H., and Burchell, H. B. Ventricular septal defect simulating patent ductus arteriosus, Proc. Staff Meet. Mayo Clin 25:69 1950.
10 Burchell, H. B and Edwards J E. Aortic sinus aneurysm with communications into right ventricle and associated ventricular septal defect, Proc Staff Meet. Mayo Clin. 26:336, 1951
11 Lin, T K., Crockett, J E., and Dimond, E. G. Ruptured congenital aneurysm of the sinus of Valsalva, Am. Heart J 51:445 1956.
12. Falholt, W and Thomsen, G Congenital aneurysm of the right sinus of Valsalva diagnosed by aortography Circulation 8:549 1953
13 Morrow A G., Baker R. R., Hanson, H F and Mattingly T W Successful surgical repair of a ruptured aneurysm of the sinus of Valsalva, Circulation 16:533 1957
14. Duras, P F Heart block with aneurysm of the aortic sinus Brit. Heart J 6:61 1944
15 Herson, R. N and Symonds, M Ruptured congenital aneurysm of the posterior sinus of Valsal a, Brit Heart J 8 125 1949
16. Oram S., and East, T Rupture of aneurysm of aortic sinus into the right side of the heart, Brit. Heart J 17:541 1955
17 Semler H J and Brandenburg, R. O Demonstration of site of rupture of aortic sinus aneurysm, Proc Staff Meet Mayo Clin 33:604 1958
18 Wood, A. M Perforation of the interventricular septum due to cardiac infarction, Brit. Heart J 6:191 1944
19 Philip, W M Rupture of the interventricular septum in myocardial infarction Brit Heart J 16:321 1954
20 Malone, R. G S., and Parker W E. Rupture of the interventricular septum, Brit. Heart J 1 :445 1955
21 Smith, J C Rupture of a papillary muscle of the heart report of two cases, Circulation 1 766 1950
22 Nicholson, R. E Syndrome of rupture of aortic aneurysm into the pulmonary artery: reviews of the literature with report of two cases, Ann. Int Med. 19:286 1943
23 Dadds, J H and Hoyle C Congenital aortic septal defect, Brit. Heart J 11:390 1949
24 Scott, H W and Sabiston, D C Surgical treatment for congenital aorticopulmonary fistula J Thoracic Surg 25:26, 1953
25 Brown, R. C and Burnett D Anomalous channel between aorta and right ventricle, Pediatrics 3:597 1949
26 Mozen, H E Congenital cirsoid aneurysm of a coronary artery with associated aortico-atrial fistula treated by operation, Ann. Surg 144:219 1956
27 Davis, C J Dillon R F Fell, E H and Gasul, B M Anomalous coronary artery simulating patent ductus arteriosus, J A M A 160 1047 1956
28. Davison, P H McCracken B H and McIlveen D J S Congenital coronary arterio-venous aneurysm Brit. Heart J 1 :569 1955
29 Brown J W Heath, D and Whitaker W Cardio-aortic fistula a case diagnosed during life and treated surgically Circulation 12:819 1955
30 Dubost, C Blondeau, P and Piwnica, A. Ruptur des anevrysmes des sinus de Valsalva dans les cavités cardiaques, J chir 75:539 1958
31 Sakakibara, S and Konno, S Operation of congenital aneurysm of sinus of Valsalva (In Japanese) Operation 14 725 1960
32. Brofman, B L and Elder J C Cardio-aortic fistula (temporary circulatory occlusion as an aid in diagnosis) Circulation 16:77 1957
33 Kimoto, S Cardiac surgery (In Japanese) Tokyo 1959 Kanehara & Co pp 285
34. Fowler R. E L., and Bevil, H H Aneurysm of the sinuses of Valsalva with report of a case Pediatrics 8:340 1951
35 Douglas, C H Ha e, M and White, H. J Cardio-aortic fistulas and aneurysms of sinus of Valsalva in infancy Pediatrics 27:415 1961
36 Spencer F C., Blake H. A., and Bahnson, H T Surgical repair of ruptured aneurysm of sinus of Valsalva in two patients, Ann. Surg 152:963 1960.

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Operation

Types IIIa and II Surgical correction of these types of aneurysms under hypothermia[13,25] is possible but the combined use of the artificial heart lung is safer[3,4,26] The lesion can be successfully repaired by closure of the aneurysm at its base with continuous or interrupted sutures

Type IIIv We have not had any experience with this type but Lillehei and Bigelow[3] have obtained good results by suturing the base of the aneurysm using extracorporeal circulation and entering the heart through the right ventricle.

Type I For this type, the operative procedure followed in Case 6[1] of our series will be described Using moderate hypothermia and the heart lung apparatus, we incised the right ventricle and root of the aorta disclosing the origin of the aneurysm from the right coronary sinus. After the aneurysm had been excised the defect was sutured and closed and care was taken not to injure the coronary artery For good measure this area was reinforced with an Ivalon patch placed from the aortic to the right ventricular side. Adequate results have been obtained with this procedure but evaluation of this method will have to await additional investigation since this is the only case in which operation has been carried out.

Type IVSD This type of aneurysm is very difficult to manage surgically We have had a disagreeable experience with one case which ended fatally when rupture recurred postoperatively Many failures have also been reported in the literature[21,22] The surgical procedure is complicated by the fact that the upper border of the aneurysm is formed by a part of the fragile tissue of the sinus so that there is, therefore no strong support for the sutures, and by the fact that the interventricular septal defect must also be closed when the aneurysm is excised In addition complete correction of the deformed aortic valve cannot be hoped for In our series of cases those in which the lesions were of Stage 2 or less in severity were managed by insertion of the aneurysm into the left ventricle and closure of the ventricular septal defect which improved the aortic insufficiency to some extent.

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REFERENCES

1. Sakakibara, S., and Konno, S. Congenital aneurysm of sinus of Valsalva. Anatomy and classification, Am. Heart J 63:405 1962.
2. Jones A. M and Langley F A. Aortic sinus aneurysm, Brit. Heart J 11:325 1949
3. Bigelow W G and Barnes, W T Ruptured aneurysm of aortic sinus, Ann. Surg 150 117 1959
4. Lillehei, C W., Stanley P and Varco, R. L. Surgical treatment of ruptured aneurysm of the sinus of Valsalva, Ann. Surg 146:459 1957
5. Venning, G R. Aneurysm of the sinus of Valsalva, Am. Heart J 42:57 1951
6. Macleod, A.: Cardio-aortic fistula Brit. Heart J 6 194 1944
7. Hauser H Aneurysma des Sinus Valsalvae mit Durchbruch in den rechten Vorhof Deutsche Ztschr ges. gerichtl. Med. 32:490, 1940.
8. Kawasaki, I A., and Benenson, A. S. Rupture of an aneurysm of a sinus of Valsalva into

the right auricle, Ann. Int. Med. 25:150, 1946
9 Morgan, E. H., and Burchell, H. B Ventricular septal defect simulating patent ductus arteriosus, Proc. Staff Meet. Mayo Clin. 25:69 1950.
10 Burchell, H B and Edwards J E. Aortic sinus aneurysm with communications into right ventricle and associated ventricular septal defect, Proc. Staff Meet. Mayo Clin 26:336, 1951
11 Lin, T K., Crockett, J E., and Diamond, E. G Ruptured congenital aneurysm of the sinus of Valsalva, Am. Heart J 51:445 1956
12 Falholt, W and Thomsen, G. Congenital aneurysm of the right sinus of Valsalva, diagnosed by aortography Circulation 8:549 1953
13 Morrow A. G., Baker R R., Hanson, H F and Mattingly T W: Successful surgical repair of a ruptured aneurysm of the sinus of Valsalva Circulation 16:533 1957
14. Duras, P F Heart block with aneurysm of the aortic sinus Brit. Heart J 6:61 1944.
15 Herson, R. N and Symonds, M Ruptured congenital aneurysm of the posterior sinus of Valsalva, Brit Heart J 8 125 1949
16 Oram, S., and East, T Rupture of aneurysm of aortic sinus into the right side of the heart, Brit. Heart J 17:541 1955
17 Semler H J and Brandenburg R. O Demonstration of site of rupture of aortic sinus aneurysm Proc Staff Meet Mayo Clin 33:604 1958
18. Wood, A M Perforation of the interventricular septum due to cardiac infarction, Brit Heart J 6 191 1944
19 Philip W M Rupture of the interventricular septum in myocardial infarction Brit Heart J 16:221 1954
20 Malone, R G S and Parker W E. Rupture of the interventricular septum, Brit Heart J 1 :445 1955
21 Smith, J C Rupture of papillary muscle of the heart report of two cases, Circulation 1 766 1950
22 Nicholson, R. E. Syndrome of rupture of aortic aneurysm into the pulmonary artery review of the literature with report of two cases, Ann. Int Med. 19:286 1943
23. Dadds, J H and Hoyle, C Congenital aortic septal defect Brit. Heart J 11:390 1949
24. Scott, H. W., and Sabiston, D C. Surgical treatment for congenital aorticopulmonary fistula J Thoracic Surg 25:26, 1953
25 Brown, R. C. and Burnett, D Anomalous channel between aorta and right ventricle Pediatrics 3:597 1949
26 Moren H E Congenital cirsoid aneurysm of a coronary artery with associated arterio-atrial fistula treated by operation, Ann. Surg 144:219 1956
27 Davis, C J., Dillon, R. F Fell, E. H and Gasul, B M Anomalous coronary artery simulating patent ductus arteriosus J A.M A. 160 1047 1956
28. Davison, P H., McCracken, B H and McIlveen, D J S Congenital coronary arteriovenous aneurysm Brit. Heart J 17:569 1955
29 Brown, J W Heath D and Whitaker W Cardio-aortic fistula a case diagnosed during life and treated surgically Circulation 12:819 1955
30 Dubost, C Blondeau, P and Piernica, A.: Rupture des anevrysmes des sinus de Valsalva dans les cavités cardiaques, J chir 75:539 1958
31. Sakakibara, S and Konno, S Operation of congenital aneurysm of sinus of Valsalva (in Japanese) Operation 14 723 1960
32. Brofman, B L., and Elder J C Cardio-aortic fistula (temporary circulatory occlusion as an aid in diagnosis) Circulation 16:77 1957
33 Kimoto, S Cardiac surgery (in Japanese) Tokyo, 1959 Kanehara & Co pp. 283
34. Fowler R E L., and Bevil, H H Aneurysm of the sinuses of Valsalva, with report of a case Pediatrics 8:340 1951
35 Douglas, C H Hara, M and White, H J Cardio-aortic fistulas and aneurysms of sinus of Valsalva in infancy Pediatrics 27:415 1961
36 Spencer F C Blake H A and Bahnson, H T Surgical repair of ruptured aneurysm of sinus of Valsalva in two patients, Ann Surg 152:963 1960

Arteriosclerosis in high-pressure and low-pressure coronary arteries

In spite of recent emphasis on the role of lipids in the pathogenesis of arteriosclerosis, an increase in arterial pressure is one factor which is concerned with the pathogenesis of arteriosclerosis. Many examples of the etiological relationship of hypertension to the development of arteriosclerotic lesions have been cited. We wish to describe an interesting and almost ideal "experiment" performed by nature which lends further support to the importance of intravascular pressure in the pathogenesis of arteriosclerosis.

Occasionally one coronary artery arises from the pulmonary artery, while the other coronary artery arises in a normal manner from the aorta. Usually it is the left coronary artery which arises from the pulmonary artery. This anomaly is rarely compatible with more than a few months of life. However, we are aware of 17 instances in which patients with this defect survived until adulthood.[1] On the other hand, the opposite situation, in which the right coronary artery arises from the pulmonary artery, is compatible with normal life expectancy. This defect is exceedingly rare; only 5 cases have been reported.

Obviously, the coronary artery which arises from the aorta is subjected to much higher intravascular pressures than the one which arises from the pulmonary artery. However, the lipid content of the blood which flows through the two vessels will be identical. Thus, nature has established a well-controlled experiment which consists of a coronary artery that contains blood at low pressure and in the same heart a coronary artery in which the intravascular pressure is high. Fortunately, this important experimental preparation has been allowed to go on for many years of life in a small group of people. Furthermore, nature has varied the "experiment" so that in some instances the right coronary artery is the high-pressure artery, whereas in other instances the left coronary artery is the high-pressure one. A study of the necropsy material from patients with these anomalies was all that was needed to reap the fruit of the "experiment."

When the left coronary artery originates from the pulmonary artery, the vessel is arterial in nature but thin walled and in some respects vein-like, whereas the right coronary artery is thick walled, tortuous, and has the usual histologic characteristics of a coronary artery. The left anomalous coronary artery may show intimal hyperplasia, thickening of the internal elastic membrane, and thinning of the media due to loss of smooth muscle, but atheromata are not seen. However, in the same patient the right coronary artery, which arises from the aorta, may show streaks and spots of atheroma, or even marked arteriosclerosis.[1]

When the right coronary artery arises from the pulmonary artery, then this vessel is thin walled and free of atheroma, whereas the left coronary artery, which arises from the aorta, is thick walled and has arteriosclerotic changes.

The degree of coronary arteriosclerosis was greatest in those instances in which the left coronary artery originated from the aorta. This is probably due to the fact that the patients with this lesion survived longer (average, 62 years) than did the 17 patients in whom the right coronary artery arose from the aorta, who attained an average adulthood of 35 years. In fact, one patient in whom the left coronary artery arose from the aorta and the right coronary artery arose from the pulmonary artery survived to 90 years of age. The left coronary artery of this patient was markedly arteriosclerotic, whereas the right coronary artery was completely free of arteriosclerosis[2] in spite of his extreme age.

These observations show that intravascular pressure is of paramount importance in the formation of arteriosclerotic lesions. The severity of the lesions is also shown by these "experiments" of nature to be directly related to the duration of time over which the pressure acts. Certainly, the lipid state must have been the same for the coronary vessel with anomalous origin as for the vessel with the normal origin. It is unlikely that differences in oxygen content between the two arteries was a significant factor since atheroma form in the pulmonary arteries when pulmonary hypertension develops. The thickened intima of the anomalous artery should tend to encourage rather than discourage the formation of atheroma. Thus one is led to the logical conclusion that the low intravascular pressure in the coronary artery which originated from the pulmonary artery "protected" the vessel from arteriosclerosis, the lipid content of the blood circulating within the vessel notwithstanding.

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REFERENCES

1. Burch, G. E., and Phillips, J. H.: Hypertension and arteriosclerosis, Am. Heart J. 60:163, 1960.
2. Burch, G. E., and DePasquale, N. P.: Anomalous coronary arteries. (To be published.)
3. Dietrich, W.: Ursprung der vorderen Kranzarterie aus der Lungenschlagader mit ungewöhnlichen Veränderungen des Herzmuskels und der Gefässwände, Arch. path. Anat. 303:436, 1938.
4. George, J. M., and Knowlan, D. M.: Anomalous origin of the left coronary artery from the pulmonary artery in an adult, New England J. Med. 261:993, 1959.
5. Gouley, B. A.: Anomalous left coronary artery arising from pulmonary artery (adult type), Am. Heart J. 40:630, 1950.
6. Cronk, E. S., Sinclair, J. G., and Rigdon, R. H.: Anomalous coronary artery arising from pulmonary artery, Am. Heart J. 42:906, 1951.

More efficient dialysis

Hemodialysis is now generally accepted as an integral part of the treatment of the more severe forms of acute renal failure, but a healthy interest in developing improved apparatus remains. The efficiency of a new rotating-drum artificial kidney with a surface area of cellophane of 3.2 square meters, has been assessed[2] in 10 patients undergoing dialysis for the treatment of acute renal failure of various etiologies. Efficiency was assessed on the basis of percentage fall in the levels of plasma urea, total urea removed from the rinsing fluid, and clearance of urea. This was supplemented by studies on the removal of three other more slowly diffusible metabolites—creatinine, uric acid, and inorganic phosphate—which are perhaps of more importance than urea in the complex biochemical disorder of uremia. The studies clearly show that significantly larger amounts of diffusible metabolites can be removed by this new apparatus in 4½ hours of dialysis than by the twin-coil disposable artificial kidney in 6 hours, and as much in 3 hours.

Increased efficiency has been achieved without prolonging the time required to assemble the machine, and without increasing the amount of priming blood required (1,080 ml.). The initial cost of the machine is higher than for the twin-coil apparatus but is soon offset by the much lower running costs (about one tenth) for the disposable parts.

Short, effective dialyses are less fatiguing for the patient and less time-consuming for the staff and dialysis has to be performed less often. These considerations are particularly cogent in cases in which catabolism is intense. In addition to these immediate considerations it is hoped that the use of a more efficient dialyzer may lead to a further reduction in the mortality due to acute tubular necrosis, especially that of surgical origin, the variety which currently has the worst prognosis.

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REFERENCES

1. Parsons, F. M., Hobson, S. M., Blagg, C. R., and McCracken, B. H.: Optimum time for dialysis in acute reversible renal failure. Description and value of an improved dialyser with large surface area, Lancet 1:129, 1961.
2. Kennedy, A. C., Gray, M. J. B., Dunwoodie, A., and Linton, A. L.: Removal of urea, creatinine, uric acid, and inorganic phosphate by a rotating-drum artificial kidney, Lancet 2:996, 1961.

Binding and storage

It has become apparent from the recent investigations that the physiologic activity of many substances is modified by the process of binding and storage. Binding is conceived of as a loose chemical bond between the active substance and a blood or tissue constituent, usually a protein, whereas storage implies cellular participation in the inactivation and in the subsequent release of the active [illegible] The distinction is largely a semantic one since the process of storage always requires binding and merely implies more elaborate chemical processes, which are usually intracellular. Both words imply that the substances bound or stored will be available for subsequent release chemically intact.

The tissue specificity of this binding or storage [illegible]

astonishing. For example, it has been shown that after sympathectomy norepinephrine is bound to the tissues only on the nonsympathectomized side which thus suggests specific storage in sympathetic nerve tissue. The reticuloendothelial system and the liver the storage capacities of which have been studied extensively are, therefore, not the only tissues capable of exercising this function. Moreover extracellular binding to specific plasma proteins has been demonstrated for insulin, which is bound by specific antibodies, as well as for other hormones, such as thyroxin.[3]

It has recently been emphasized that binding substances play an important role in the activity of such neurohumors as acetylcholine, serotonin[4] and norepinephrine. Yet little is known of the nature of these binding substances or of their activity. It is conceivable that chemical defects in, or deficiencies of such substances, which are often protein in nature may be involved in the etiology of certain obscure diseases, such as myasthenia gravis and essential hypertension.

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REFERENCES

1. Herthing, G., Axelrod, J., Kopin, I. J., and Whitby, L. G.: Lack of uptake of catecholamines after chronic denervation of sympathetic nerves, Nature 189:66, 1961.
2. Berson, S. A., and Yalow, R. S.: Plasma insulin in health and disease, Am. J. Med. 31:874, 1961.
3. Taurog, A., and Chaikoff, I. L.: The nature of the circulating thyroid hormone, J. Biol. Chem. 176:639, 1948.
4. Nachmansohn, D.: Chemical factors controlling nerve activity, Science 134:1962, 1961.
5. Hess, S. M., Connamacher, R. H., Ozaki, M., and Udenfriend, S.: The effects of alpha methyl-dopa and alpha-methyl-metatyrosine on the metabolism of norepinephrine and serotonin in vivo, J. Pharmacol. & Exper. Therap. 134:129, 1961.
6. Gitlow, S. E., Mendlowitz, M., Smith, A., Gall, E., Wolf, R. L., and Naftchi, N. E.: The dynamics of norepinephrine metabolism, *in* Brest, A. N., and Moyer, J. H., editors, Hypertension, recent advances. The Second Hahnemann Symposium on Hypertensive Diseases, Philadelphia, 1961, Lea & Febiger, p. 335.
7. Grob, D.: Muscular disease, Bull. New York Acad. Med. 37:809, 1961.
8. Mendlowitz, M., Gitlow, S. E., and Naftchi, N.: The etiology of hypertension, *in* Mendlowitz, M., editor: Hypertension. New York, 1961, Grune & Stratton, Inc.

Damage to the aortic valve as a cause of death in bacterial endocarditis

The most common cause of death in patients with bacterial endocarditis is heart failure. Bacteriologic cure is generally easily achieved with antibiotics, and complications, such as renal failure, cerebral embolism, and rupture of mycotic aneurysms, are unusual. Heart failure in bacterial endocarditis results mainly from (1) myocarditis, (2) coronary embolism, and (3) valvular deformity. A particular kind of valvular deformity perforation or erosion of the aortic valve was the most common cause of death from bacterial endocarditis at Grace-New Haven Community Hospital during the past 5 years.

Aortic insufficiency was present upon admission, or developed shortly thereafter in 15 of the 33 patients who had proved bacterial endocarditis. In 5 patients with aortic insufficiency at the time of initial examination, new damage may have occurred in 4 but could not be documented because the patient survived. The other 10 patients had aortic insufficiency due to recent valvular damage: this was demonstrated in 7 at autopsy whereas in 3 the signs developed while the patients were under observation. Of the 7 instances of valvular damage demonstrated at autopsy 3 were perforations (one due to *Streptococcus fecalis* and two to alpha hemolytic streptococci), and 4 were severe ulcerations (one due to *Streptococcus fecalis* one to *Staphylococcus albus* and two to *Staphylococcus aureus*).

Although the mortality in this series was 39 per cent, death ensued in 54 per cent of the patients with aortic insufficiency and in only 28 per cent of the patients with other valvular lesions. This mortality was not due to failure of treatment since bacteriologic cure was achieved in all but 2 patients from each group. Similar microorganisms were recovered from the blood streams of patients with and without aortic insufficiency. Differences due to age or to the length of time between onset of symptoms and start of therapy could not be detected between patients with and those without aortic insufficiency. There seemed to be a difference in sex incidence since males predominated, 12 to 3 in the group with aortic insufficiency whereas females were in the majority 13 to 5 in the group without aortic insufficiency. Six patients were found at autopsy to have developed endocarditis *in the absence* of underlying valvular disease.

The importance of damage to the aortic valve in producing congestive heart failure, thereby determining the prognosis of bacterial endocarditis,

has been appreciated for many years.[3] It is only since the advent of effective antibiotics, however that this lesion has attained prominence. Although many authors have believed that endocarditis most often aggravates existing aortic regurgitation, there is evidence which suggests that new damage is frequently unrecognized. One explanation why new damage to the aortic valve may be overlooked clinically is the rapidity with which severe valvular damage occurs, even when caused by relatively benign organisms such as alpha hemolytic streptococci.

Early diagnosis based on a high level of suspicion still provides the most practical approach to prevention of the complications which result from bacterial infection of the heart valves. The poor prognosis of aortic insufficiency acquired as a result of bacterial endocarditis requires that early consideration be given to the possibility of surgical correction of the valve defect, particularly in patients without known underlying heart disease.

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REFERENCES

1. Kerr, A., Jr.: Subacute bacterial endocarditis, Springfield, Ill., 1955, Charles C Thomas, Publisher, p. 236.
2. Jones, A. M., Herring, R., Langley, F. A., and Oleisky, S.: Penicillin treatment of subacute bacterial endocarditis, Brit. Heart J. 9:38, 1947.

Announcements

The American College of Physicians has announced a schedule of postgraduate courses to be presented throughout the country in the second quarter of 1962. The courses are part of the postgraduate program of the American College of Physicians, and are aimed at providing practicing physicians with current information on advances in internal medicine and related specialties. The second quarter 1962 courses and their directors are:

May 14-16: Course No. 12, FUNDAMENTAL AND APPLIED ASPECTS OF CARDIOLOGY, Wayne State University College of Medicine, Detroit, Mich. Richard J. Bing, M.D., F.A.C.P., Director. Minimal registration 40, maximal registration, 200.

May 21-25: Course No. 13, THE NEUROLOGY OF DISEASES OF INTERNAL MEDICINE, Harvard Medical School, Boston, Mass. Raymond D. Adams, M.D., Director.

June 4-8: Course No. 14, PSYCHIATRY FOR THE INTERNIST, The Psychiatric Institute, University of Maryland School of Medicine, Baltimore, Md. Ephraim T. Lisansky, M.D., F.A.C.P., Director.

The proceedings of a conference on MECHANISMS OF EXPERIMENTAL RENAL HYPERTENSION, held in April, 1961, in Augusta, Michigan, are now available in reprint form.

The program, with Sibley W. Hoobler, M.D., as Chairman, and A. C. Corcoran, M.D., as Vice Chairman, included reviews of the following topics: physiologic mechanisms (renin, liver, adrenal, kidney); vessel wall changes (reactivity of arterioles, arteriolar rigidity, effect of hypertension on vessel walls); humoral substances (antihypertensive substance from kidney, anephrotensin, angiotensin, renin).

Copies can be obtained without charge from Walter Freyburger, M.D., the Upjohn Company, Kalamazoo, Michigan.

PHYSIOLOGY AND PSYCHOLOGY OF WORK RELATING TO CARDIACS: A postgraduate course on the basic physiology and psychology of work relating to cardiovascular patients has been scheduled for June 18-22, 1962, at the Tudor Arms Hotel, Carnegie at East 107th St., Cleveland, Ohio.

The objective of the course, to be conducted as a workshop limited to 150 participants, will be to explore further the problem of assessing medically the physical types of activity suited to an individual with heart disease, the factors involved, and how to determine them.

The course is being conducted jointly under the auspices of the American Heart Association, the Cleveland Area Heart Society, Heart Disease Control Program of the U. S. Public Health Service, and Western Reserve University. Laboratory facilities of the University and affiliated hospitals will be utilized for field visits during the sessions. This practical course will include lectures, demonstrations, individual participation and testing, problems, and group discussion.

In addition to a thorough study of techniques for evaluating circulatory and total body functions, the workshop will explore the following subjects: "Physiology of Effort," including cardiac response to muscular work, various magnitudes, duration, etc.; effects of nutrition, effects of disease upon ability to perform muscular work of the heart, lungs, and of other symptoms, and the "Physiology of Emotional Stress"; also, the "Psychologic and Psychiatric Aspects" and "Characterization and Requirements of Work," which will embrace caloric, thermal, psychologic, and vocational aspects, environment of the factory, farm or office, fatigue, and on-the-job studies in the field.

Those who wish to attend the course or obtain further information may write to Herman K. Hellerstein, M.D., Cleveland Area Heart Society, 1689 East 115th St., Cleveland 6, Ohio.

THE XIV INTERNATIONAL CONGRESS OF SPORT MEDICINE will be held at the Hotel Carrera, 180 Teatinos St., Santiago, Chile, on May 23, 24 and 25, 1962.

For more information, contact Dr. René Miranda T., General Secretary, P.O. Box (Casilla) 9439, Santiago, Chile.

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Editorial

Maldevelopment and the heart

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Understanding of cardiovascular anomalies began with the occasional autopsy studies of the early sixteenth century and rapidly developed as postmortem dissection became more widely practiced. Notable among early records was the description by Niels Stensen (1638-1686) of defects known today as the tetralogy of Fallot.

The largely morphologic approach of the early investigators was broadened by the development of serious theoretical concepts, such as those of Karl Rokitansky (1804-1878)

> Malformations . . . are deviations of the organism or of an organ so intimately blended with its primary development, as to occur only at the earliest periods of embryonic life or at any rate before that of mature foetal existence.
>
> The opinions of modern physiologists on [the genesis of malformation] may be collected under two heads. According to the one section the malformations are referable to a primitive malformation of the germ. According to the other to various influences affecting the germ in the progress of development.
>
> The second of the aforesaid propositions embraces several hypotheses . . .
>
> The more generally received one sets forth that *most malformations represent certain stages of the development of the embryo and of its organs at which stages formation has stopped short or from which ulterior development has ceased to follow the normal type.* The malformation is therefore essentially an *arrest of development.*
>
> This theory of malformations is in a great measure correct. Still it does *not* attempt to explain the *cause* of the arrest, which may be any one of those already enumerated, be it concerned with the germ with sickening of the embryo with mechanical influence or with mental emotion.
>
> A classification founded upon the occasional causes is impracticable, since the same malformation may originate from various causes.[1]

These hypotheses were supported by subsequent embryologic investigations of Franklin Paine Mall (1862-1917) of Baltimore and Sir Arthur Keith (1866-1955) of London. Mall[2] concluded that inherently pathologic ova and faulty intrauterine environments accounted for many developmental anomalies. Keith[3,4] studied the phylogenesis and comparative anatomy of the bulbus cordis in normal and abnormal cardiogenesis.

The first significant clinicopathologic cor-

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relation was that of Thomas Bevill Peacock (1812-1882) who personally studied the natural history and morbid anatomy of many cardiovascular defects. His remarks on the genesis of malformations are still pertinent:

> In all cases of malformation there must exist some primary deviation from the natural process of development upon which other secondary changes are dependent. . . . The earlier the period at which the process of development is deranged the greater will probably be the defect and the less readily will the system accommodate itself to the change after birth. So that the cases in which with any marked deviation from the natural conformation extrauterine life is maintained for a longer or shorter period probably constitute only a small proportion of those in which the development is irregular. It seems reasonable to suppose that during the earlier periods of foetal life when growth is most rapid the process would be most liable to derangement.[3]

Correlation of embryologic, clinical, and morphologic aspects of cardiovascular anomalies owes much to the work of Maude E. Abbott (1869-1940) of Montreal whose classification laid the foundations for the surgery of developmental cardiac disease.

It is difficult to overestimate the importance of the association by Norman McAlistair Gregg[6] of Sydney of congenital cataract and cardiac defects with a previous epidemic of rubella which affected mothers during early pregnancy. Subsequently confirmed by Swan and associates,[7] of Adelaide and later in other centers, this discovery indicated the importance of environmental events in early cardiogenesis, and not only emphasized the relative sensitivity of embryonic tissues during morphogenesis, but drew attention to the only known maternal infectious disease to result in such anomalies.

Experimental investigations of malformation had already been initiated over 100 years previously by the Geoffroy Saint Hilaires, of France, who produced anomalous chick embryos by subjecting eggs to various physical disturbances during early incubation.

These pioneering studies, repeated and amplified by later workers, culminated in the present considerable experimental evidence of the teratogenicity of many randomly chosen physical and chemical agents. Further additions to the list of teratogenic agents merely emphasize the importance of environmental factors in maldevelopment without significantly advancing understanding of the underlying processes. This can be furthered only by quantitative (as opposed to purely qualitative) observations of this kind, and especially by detailed studies of actual mechanisms by which anomalies of development are produced.

Experimental studies indicate that teratogenic stresses, if applied during morphogenesis, produce malformations the severity of which is proportional to the intensity and duration of the trauma induced. Usually such malformations follow exposures to test agents in concentrations which are unlikely to account for sporadic maldevelopment. Nevertheless, it may thus be possible to demonstrate stepwise both morphologic sequences and underlying mechanisms by which experimental and naturally occurring anomalies are produced. It seems likely that in most, if not all, instances the pathways concerned are principally metabolic whether or not they are determined by intermediary genetic changes.

Morphologic studies of the end results of disturbances initiated during embryogenesis cannot be expected to reveal details of the mechanisms by which these disturbances are produced. The search for these mechanisms leads directly back to events of morphogenesis and to parental contributions to conception and subsequent development. The problem is the familiar one of relating structure to function, but the levels of correlation are cellular, subcellular, and molecular. Beginning with fertilization and continuing until morphogenesis is complete, embryogenesis is concerned with morphologic and physiologic processes the dynamism of which contrasts strongly with the more rigid patterns of later development. Implicit here is a precise understanding of normal embryogenesis at these levels, for it is upon this that recognition of deviations from the normal will depend. It is appropriate to examine here some observations of normal and abnormal cardiogenesis.

Aspects of normal cardiogenesis

Structural and cytochemical analyses of fertilized eggs confirm the presence of organ forming regions at early stages of embryonic development and reveal changing localizations and chemical features of these during morphogenesis.

Although presumptive cardiogenic cells have not been located definitely before incubation evidence points to their concentration in peripheral and posterior parts of the blastoderm prior to their migration from either side toward the midline posteriorly during early development of the primitive streak. Apparently invagination from the surface of the blastoderm leads to their concentration within the streak itself shortly before that structure is fully defined Thereafter the invaginated cardiogenic material is situated bilaterally in the mesoderm on either side of the streak and is concentrated especially near the primitive node

As the head process appears these cardiac primordia elongate and the amniocardiac vesicles precursors of the pericardial cavity form by a splitting of the mesoderm into somatic and splanchnic layers the presumptive cardiac cells remain in the latter closely applied to the endoderm. Subsequent ventromedial folding of the endoderm during formation of the foregut brings the cardiac primordia toward the midline whence additional migration approximates their cephalic ends ventral to the foregut Cavitation of these gives rise to endocardial tubes progressive cephalocaudal fusion of which as can be observed in the living chick embryo leads to formation successively of the truncus arteriosus, bulbus cordis, ventricle atrium and finally the sinus venosus of the primitive tubular heart

Separation of pulmonary and systemic circulations and control of blood flow through the heart follows the development of septa and valves which convert the tubular heart of the embryo by a more or less longitudinal division associated with complex bending and torsion into the four chambered organ of maturity

Fluctuations in subsequent growth of cardiac dimension and weight are possibly related to demands made by successive developments of the vitelline and allantoic circulations and finally by the onset of pulmonary respiration

These events reflect visible cellular developments in early cardiogenesis. The earliest recognizable myocardial primordia consist of networks of loosely arranged cells with ovoid nuclei which contain 2 or 3 nucleoli At an early stage these cells proliferate become fusiform in shape and apparently form a compact syncytium

That subsequent cardiac growth is progressively less dependent on cell multiplication and more so on cell hypertrophy is indicated by decreasing density of nuclear distribution in cardiac tissue with age and by progressive reduction of mitotic activity from the second day of incubation until its virtual cessation about the tenth day after hatching

At or even before 30 hours of incubation isolated myofibrils formed from or under the influence of mitochondria, appear in increasing numbers within the cytoplasm where their differentiation continues throughout most of the incubation period [8]

Myofibrillar striations appear early but the dense substance of the A band the site of localization of the contractile protein myosin does not appear to be laid down until about 48 hours of incubation despite the onset of visible contractions at an earlier stage [9]

Myocardial autonomy and function are demonstrable in the normally developing chick embryo long before cardiogenesis is complete Beginning some 30 hours after incubation intermittent rhythmical twitchings of the right side of the ventricle develop rapidly into stronger and more regular contractions of the entire tubal heart the contraction wave is propagated anteroposteriorly always beginning in the most recently formed caudalmost portion.

These contractions soon become sufficiently strong to draw blood through the newly formed vascular system toward the heart until by the third day of incubation it flows in a continuous stream from the yolk sac through the heart to the embryo and its source of oxygen The strength and direction of this stream passing through the developing heart may exert important physical influences on the morphogenesis of internal cardiac structures.

Indications that specific metabolic

cells may be due to ameboid behavior mitotic activity or other internal changes which alter their shapes and surface areas. However in migrations of layers or masses of cells which require a certain constancy of intercellular relationships such forces are likely to be subsidiary to those which arise from the nature of cell membranes.[12] These appear to have a lipoprotein structure and to contain proteins with enzymatic and antigenic properties probably associated with nucleic acids. It is postulated that as a result of linkages between specific molecular groups at contacting surfaces cells might be bound together in enzyme-substrate or antigen-antibody fashion and that changes in cell adhesiveness, by altering areas of contact may produce changes in cell shapes of the kinds normally observed in morphogenesis.

Sodium acetate sodium citrate, acetylcholine, and especially the chelating agent Versene, all hinder fusion of the bilateral cardiac primordia and cause cardia bifida at certain concentrations and complete disaggregation at higher concentrations—effects which can be prevented by the addition of calcium. DeHaan[12] proposes that calcium is not only necessary for cell adhesion but also controls its strength and that abnormal morphogenesis may be promoted by removal of just enough calcium to disturb intercellular adhesion without completely disrupting it.

Although such observations reveal something of the intrinsic needs of developing cardiovascular tissues, they tell us little of factors which normally determine temporal and spatial sequences in cardiogenesis—factors which reside, presumably both within and beyond the morphologic limits of cardiogenic material itself Studies of embryonic induction indicate that, aside from properties intrinsic to individual cells, differentiation depends partly on influences which are available only in homogeneous cell populations of certain minimal size, and partly on influences which arise from intimate associations of those populations with others of different embryonic origin and that such influences may be related to macromolecules, such as proteins or their conjugates with nucleic acids or polysaccharides.[13]

Apart from demonstrations that cardiogenesis, in amphibian embryos at least, is dependent upon interactions between mesoderm and endoderm little can be said at present in regard to the inductive phenomena specific to development of the heart Suggestions that a similar dependence occurs in chick embryos are based on inconclusive evidence of the effects of the metabolic inhibitor antimycin A, on cardiogenesis.[3] Development of the heart and other mesodermal structures is blocked in embryos cultured with endodermal surfaces contacting media which contain this substance. However when cultured with ectodermal surfaces contacting such media neurogenesis but not cardiogenesis is affected [14]

Intrinsic cellular influences in cardiogenesis concern nucleocytoplasmic interactions with particular regard to the roles of chromosomes and the significance of their distribution evenly to all embryonic cells during development. Investigations of these problems indicate certain features which may be applicable in principle to cardiogenesis. Studies of hydridization in amphibians indicate that up to the stage of gastrulation (the stage at which differentiation and organogenesis begin) development receives no specific nuclear contribution but is controlled entirely by cytoplasmic factors. Beyond this stage, however the nucleus is essential for thereafter normal differentiation depends on a complete and balanced set of chromosomes.[15] Furthermore visible structural changes which occur in these may be closely related to genetic and physiologic activities of the cells concerned [16]

Such indications of subcellular differentiation during embryogenesis suggest that because of genetic and other modifications, nuclei and more particularly their chromosomes, exert progressively more specific, sometimes dominant, influences on the rate and direction of development Further investigations along these lines may reveal relationships between specific cardiac malformations and individual sharply localized subcellular defects.

Such studies can be facilitated by autoradiographic techniques depending on the labeling of thymidine which is incorporated in the genetic material desoxyribo acid.[17] Because such methods a

applicable to cells in tissue culture and to living animals they should clarify mechanisms of cell migration and tissue differentiation in cardiogenesis.

On morphologic grounds alone, it is clear that cardiovascular development is profoundly influenced by subtle minute and even molecular variations of the environment and that particular morphologic changes are decided by the times at which such variations occur In detail the mechanisms by which such influences operate remain obscure but certain facts have been revealed which enable hypotheses of embryogenesis and organogenesis to be made at subcellular and molecular levels. In principle the advances which have been made in no way invalidate the masterly generalizations of Karl Rokitansky and Thomas Bevill Peacock.

REFERENCES

1 Rokitansky K. A manual of pathological anatomy in 4 vols. Printed by J E. Adlard (Vol. I) and C & J Adlard (Vols. II IV) London, 1849 54 The Sydenham Society

2. Mall F P A study of the causes underlying the origin of human monsters, J Morphol. 19:3 1908.

3 Keith A The Hunterian lectures on malformations of the heart, Lancet 2:359 433 and 519 1909

Keith, A. Schorstein lecture on the fate of the bulbus cordis in the human heart, Lancet 2 1267 1924

Peacock, T B On malformations of the human heart, ed. 2 London, 1866 John Churchill & Sons.

6. Gregg, N McA.: Congenital cataract following German measles in the mother Tr Ophth. Soc. Australia 3:35 1941

7 Swan, C., Tostevin A. L., Moore B., Mayo, H., and Black, G H B Congenital defects in infants following infectious diseases during pregnancy with special reference to the relationship between German measles and cataract, deaf mutism heart disease and microcephaly and to the period of pregnancy in which the occurrence of rubella is followed by congenital abnormalities, M. J Australia 2:201 1943

8. Romanoff A L. The avian embryo, New York 1960, The Macmillan Company

9 Ebert, J D The acquisition of biological specificity in Brachet, J and Mirsky A. E. editors The cell, Vol. I Biochemistry physiology morphology New York, 1959 Academic Press, Inc., pp. 619-693

10. Brachet, J Chemical embryology New York, 1950 Interscience Publishers, Inc.

11 Spratt, N T Jr: Chemical control of development, in McElroy W D and Glass, B., editors A symposium on the chemical basis of development, Baltimore, 1958, The Johns Hopkins Press pp 629-645

12 DeHaan R. L. Cell migration and morphogenetic movements, in McElroy and Glass,[11] pp 339-377

13 Grobstein, C. Differentiation of vertebrate cells in Brachet and Mirsky [9] pp. 437-496.

14 Duffey L. M Initial events in cardiogenesis, Am. Heart J 60:848 1960

15 Briggs, R., and King T J Nucleocytoplasmic interactions in eggs and embryos, in Brachet and Mirsky pp. 537-617

16. Gall, J G Chromosomal differentiation, in McElroy and Glass,[11] pp 103-135.

17 Hughes, W L. Chromosomal replication and the dynamics of cellular proliferation—some autoradiographic observations with tritiated thymidine, in McElroy and Glass,[11] pp. 136-156

Clinical communications

The electrocardiographic recognition of left ventricular hypertrophy

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The adequacy of evidence derived from the electrocardiogram for diagnosis of hypertrophy of the left ventricle has been disputed.[1,2] Scott[1] reports over-all accuracy of such evidence to be 85 per cent, whereas Burch and his associates[2] conclude that the electrocardiogram can not be relied upon to indicate chamber enlargement. The abundance in the literature of electrocardiographic criteria of left ventricular hypertrophy (LVH) leads to further confusion. In applying most of these criteria to a given tracing, the clinician finds ambiguous opinion in regard to which criterion or combinations of criteria must be fulfilled before a diagnosis of LVH can be made with confidence. The sensitivity and specificity of various criteria are rarely mentioned.

The purpose of this study has been to examine the incidence and significance of the electrocardiographic changes in cases of hypertrophy of the left ventricle proved at autopsy in adults, and also to determine the frequency of these changes in tracings from hearts without anatomic evidence of chamber enlargement (NH). In addition, the extent to which associated digitalization and/or myocardial infarction with or without complications present, in a significant number of patients with LVH, interfere with the interpretation of the tracing is assessed. Chest x-ray films available in the great majority of cases studied were also reviewed to evaluate the reliability of the routine teleroentgenogram in demonstrating the presence of LVH.

Material and method

An attempt has been made to avoid some of the methodologic errors inherent in other anatomic-electrocardiographic correlations that may be responsible for the disparity of findings among different investigators. These include inadequate numbers of cases of anatomically proved LVH (so that the role of chance in producing a given degree of correlation is not clear),[4] failure to apply the criteria under evaluation to a control group of autopsy-verified nonhypertrophied hearts,[3] impure samples of LVH, i.e., cases complicated by associated myocardial infarction and digitalization, the effect of which on the electrocardiogram must be assessed independently.

We surveyed 316 consecutive autopsies

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Table I. Major causes of LVH in 135 autopsied cases

Cause	Number
HCVD	70
ASCVD	42
Aortic stenosis	6
Aortic insufficiency	1
Mitral insufficiency	2
Hyperthyroidism	1
Others	13
Total	135

on patients of both sexes, 18 years or older, performed by members of the Department of Pathology at The New York Hospital-Cornell Medical Center from July, 1957, to July, 1958. In each case an electrocardiogram had been taken within 6 months of death. Complete clinical, laboratory, and pathologic data were available in every instance and x-ray films of the chest in most cases. One hundred and ten cases were excluded for the following reasons: (a) anatomic evidence of right as well as left ventricular hypertrophy, (b) doubt concerning digitalization at the time the electrocardiogram was taken, (c) possibility that the myocardial infarction noted at autopsy may have occurred after the electrocardiogram was recorded, (d) presence of complicating features such as fever, anemia, electrolyte disturbance, myocardial fibrosis, pericardial disease, pulmonary pathology, pleural effusion and chest deformities—all of which may produce changes in the electrocardiogram independent of those resulting from LVH alone, and (e) agonal tracings or those with terminal arrhythmias.

In the 206 cases retained for analysis, 135 hearts from 82 male and 53 female subjects satisfied the following anatomic criteria of left ventricular hypertrophy and constitute the LVH group: (a) total heart weight in excess of the upper limits established by Zeek,[8] whose tables correct heart weight for body weight, length, age, and sex; (b) maximal thickness of the free wall of the left ventricle in excess of 14 mm.; and (c) right ventricular thickness less than 4 mm., to exclude associated right ventricular hypertrophy. The absolute weight of the hearts in the LVH group ranged from 320 to 900 grams, with a mean weight of 444 grams. Six foot chest films had been taken in 110 patients in this group.

The major conditions believed to be responsible for producing LVH (and not necessarily the immediate or contributing cause of death) included hypertensive cardiovascular disease, arteriosclerotic heart disease, rheumatic aortic stenosis and insufficiency, mitral insufficiency, and long-standing hyperthyroidism (Table I). In 13 cases there was no specific disease process which could in itself account for the hypertrophied left ventricle. This group of patients died of bacteremia, metastatic carcinoma, hepatic cirrhosis,

Table II. Major causes of death in 71 patients without LVH

Cause	Number
Malignancy	49
ASCVD	6
Cirrhosis	7
Renal failure	2
Tuberculosis	1
Pemphigus	1
Lupus erythematosus	1
Peritonitis	1
Endocarditis	1
Hemorrhage	1
Embolism	1
Total	71

Table III. Subdivision of LVH and NH hearts according to associated complications

Clinical type	LVH		NH	
	Number	Per cent	Number	Per cent
Uncomplicated	45	33	49	69
Infarction	25	19	9	13
Digitalization	27	20	12	17
Digitalization and infarction	38	28	1	1
Total	135	100	71	100

Table IV Criteria for left ventricular hypertrophy (Sokolow and Lyon[7])

Standard leads

1 $R + S_{III}$ = or greater than 25 mm.
2. S-T depression of 0.5 mm. or more in Lead I
3. T negative or flat, when combined with S-T depression and a tall R wave in Lead I

Unipolar limb leads

4. R in aV_L greater than 11 mm. (in a horizontal heart) or R in aV_F greater than 20 mm. (in a vertical heart)
5. S-T depression greater than 0.5 mm. in aV_L or aV_F
6. T wave in aV_L or aV_F flat or negative when accompanied by S-T depression and an R wave greater than 6 mm. in amplitude

Precordial leads

7. R_{V5} or R_{V6} greater than 26 mm.
8. S-T depression greater than 0.5 mm.
9. T waves flat or negative in V_{4-6} when accompanied by S-T depression, normal R, and small S waves
10. Intrinsicoid deflection over V_6 = or greater than 0.06 second
11. R or R_V + S_{V1} greater than 35 mm.

acute leukemia or ruptured intracranial aneurysm.

The "nonhypertrophied" (NH) group consisted of 71 hearts from 37 male and 34 female subjects which met none of the anatomic criteria of left or right ventricular hypertrophy enumerated above. Total heart weight was within the limits of normal defined by Zeek and the greatest left and right ventricular thicknesses were less than 15 and 5 mm. respectively. The absolute heart weight in the control nonhypertrophied group ranged from 140 to 410 grams with a mean weight of 301 grams. Six-foot chest films had been taken in 62 of the 71 patients in this group. The major causes of death included malignancy, arteriosclerotic heart disease, hepatic and biliary cirrhosis, renal failure, tuberculous peritonitis, pemphigus, pneumococcal endocarditis, exsanguination, embolism, and systemic lupus erythematosus (Table II).

The LVH and NH groups were each subdivided with respect to (a) digitalization at the time the tracing was recorded and (b) anatomic evidence of myocardial infarction at necropsy (Table III). "Uncomplicated" refers to those hearts, in both the LVH and NH groups in which there was no anatomic evidence of infarction or history of digitalization. There were 45 such cases with LVH and 49 without ventricular hypertrophy. "Infarction" includes 25 cases of LVH and 9 cases of NH in which there was anatomic evidence of myocardial infarction. "Digitalization" refers to 27 subjects with LVH who had been receiving digitalis, and 12 without cardiac hypertrophy who had been digitalized at the time their electrocardiograms were recorded. "Digitalization and infarction" includes 38 patients with LVH and 1 without hypertrophy who were digitalized and in whom there was in addition anatomic evidence of myocardial infarction.

Careful review of the literature revealed that within the 11 electrocardiographic

Table V Number of electrocardiographic criteria of LVH satisfied in LVH and NH hearts

Number of criteria fulfilled	*LVH*		*NH*	
	Number	*Per cent*	*Number*	*Per cent*
0	53	39	50	71
1	11	8	6	8
2	11	8	8	11
3–6	48	36	7	10
7–11	12	9	0	0
Total	135	100	71	100

Table VI LVH and NH hearts fulfilling 0-2 and 3 or more electrocardiographic criteria of LVH

Number of criteria fulfilled	*LVH*		*NH*	
	Number	*Per cent*	*Number*	*Per cent*
3–11	60	44	8	11
0–2	75	56	63	89
Total	135	100	71	100

χ^2 = 9.31, significant between 0.01 and 0.001.

Table VIIA. Number of hypertrophied and nonhypertrophied hearts meeting each component criterion

Criterion of RS-T depression	LVH: Number of positive responses	LVH: Per cent of total number of hearts (135)	LVH: Per cent of total positive responses (386)	NH: Number of positive responses	NH: Per cent of total number of hearts (71)	NH: Per cent of total positive responses (63)
I	71	53	18	16	22	25
aV_L	43	32	11 } 46	12	17	19 } 63
V	63	46	16	12	17	19
Increased oltage						
R + S	19	14	5	1	1	2
R	23	17	6	2	3	3
R ( )	9	7	2 } 18	2	3	3 } 13
S + R ( )	19	14	5	3	4	5
T w e abnormalities						
I	48	36	12	6	8	10
aV_L	36	27	9 } 33	5	7	8 } 24
V-V	46	34	12	4	6	6
Ventricular activation time	10	7	3 3	0	0	0
Total	386		100	63		100

*Further analyses to associate component with hearts may be necessary

iteria for LVH set down by Sokolow and yon[7] are embodied the important measurements most widely used to detect LVH in the routine 12 lead electrocardiograms (Table IV). These include (a) increased voltage of the QRS complex, (b) RS-T-segment depressions, (c) T wave lowering, diphasia or inversion, and (d) the duration of the intrinsicoid deflection in Leads V_5 or V_6. Consequently the criteria of Sokolow and Lyon were used in the study. They were applied first to the LVH and NH groups as a whole and then to each of the clinical subtypes within these two groups (Table III) so that the role of digitalis and myocardial infarction might also be assessed.

Results

Accuracy of all criteria in total sample. The over-all accuracy of the criteria in the LVH and NH hearts without correction for the effect of digitalization and or myocardial infarction is indicated in Table V. Of 135 cases of LVH, 53 (39 per cent) failed to meet a single one of the 11 criteria used. Among the 71 NH hearts 21 (29 per cent) manifested one or more of the electrocardiographic abnormalities indicative of LVH.

The optimal number of criteria to be satisfied in order to obtain maximal correct identification of hearts with LVH and at the same time a minimal number of false positive results in the NH group was found to be 3. Thus Table VI indicates that if any 3 or more of the 11 criteria are to be satisfied before an electrocardio-

Table VIIB. Sensitivity and specificity of individual criteria of LVH in total sample

Criterion	Sensitivity (%)	Specificity (%)
RS-T depression	45.5	27.5
QRS voltage	18.0	87.3
T wave changes	36.0	76.1
Ventricular activation time	7.4	100.0

gram may be said to reflect LVH 60 (44 per cent) of the 135 hearts with LVH will be correctly identified. Among the 71 NH cases, 8 (11 per cent) will still be falsely designated as having LVH

Sensitivity and specificity of individual criteria. The sensitivity and specificity of the 11 individual criteria were assessed in order to determine which electrocardiographic changes are the most reliable indicators of LVH and least likely to be found in NH hearts. Table VIIA indicates the number of positive responses to each criterion in the LVH and NH samples. Note that in the LVH group the total number of positive *responses* (386) exceeds the number of *cases* (135) since some of the cases satisfied more than one criterion. Among the 71 NH hearts there were 63 false-positive responses Table VIIB summarizes the sensitivity and specificity of each of the individual criteria of LVH in the total LVH and NH sample.

RS-T DEPRESSION RS-T-segment depression greater than 0.5 mm. in Leads I aV_L, and in the precordial leads accounted for the largest number 40 (63 5 per cent) of the 63 false-positive responses in the NH group. These depressions occurred with the same frequency in the extremity leads and in the precordial leads.

In addition to being responsible for the greatest number of false positive responses, RS-T-segment depression also accounted for 176 (45.5 per cent) of 386 true-positive findings in hearts with LVH In this latter group, Lead I showed a higher incidence of RS-T depression than did Lead aV_L or the precordial leads.

QRS VOLTAGE INCREASE. As noted in Table IV the criteria for increased voltage of the QRS complex embrace the standard bipolar limb leads ($R_1 + S_3 > 25$ mm) the augmented unipolar limb leads ($R_{AVL} > 11$ mm in electrically horizontal hearts and $R_{AVF} > 20$ mm. in electrically vertical hearts) and the precordial unipolar leads ($S_{V1} + R_{V5}$ or $R_{V6} > 35$ mm. R_{V5} or $R_{V6} > 26$ mm.) Such increased amplitude of QRS accounted for 8 (12 7 per cent) of the 63 false-positive scores and was present in 70 (18 per cent) of the 386 true positive responses In terms of the reliability of the individual voltage criteria among the 135 cases of LVH note that the sum of $R_1 + S_3$ exceeded 25 mm in 19 cases (14 per cent) of the total LVH sample with one false-positive response R amplitude in Lead aV_L was greater than 11 mm. in 23 cases (17 per cent) of the LVH sample with 2 false positive responses the sum of $S_{V1} + R_{V5,6}$ was in excess of 35 mm in 19 cases (14 per cent) of LVH with 3 false positive responses. The voltage criterion which demanded that the amplitude of the R wave in Leads V_5 or V_6 exceed 26 mm. gave only 9 correct responses (6.6 per cent) in the LVH group, with 2 false-positive responses. Thus, with the exception of this latter criterion, results from the 3 individual voltage criteria were very similar in their sensitivity and specificity

T WAVE CHANGES. Abnormalities of the T wave, isolated or in combination with other electrocardiographic changes, were responsible for scoring 140 (36 per cent) of the 386 correct responses in the LVH

Table VIII Response to electrocardiographic criteria for LVH in hearts with and without myocardial infarction and digitalis

Clinical type	*LVH*			*NH*		
	Per cent meeting none	*Per cent meeting one or more*	*Total number*	*Per cent meeting none*	*Per cent meeting one or more*	*Total number*
Uncomplicated	64	36	45	87	13	49
Infarction	43	57	23	43	55	9
Digitalization	26	74	27	25	75	12
Digitalization and infarction	13	87	38	0	100	

Table IXA The influence of digitalization and myocardial infarction on individual component criteria in each of the clinical subtypes (LVH)

Criterion	Clinical type (LVH)				Total number of cases
	Uncomplicated	Infarction	Digitalization	Digitalization and infarction	
Total	45	25	27	38	135
Voltage					
$R_1 + S_3$	5 11%	4 16%	5 19%	5 13%	19
R_{aVL}	6 13%	4 16%	6 22%	7 18%	23
R_{V5} (V_6)	3 7%	2 8%	1 4%	3 8%	9
S_{V1} + R_{V5} (V_6)	7 15%	2 8%	6 22%	4 11%	19
RS-T segments					
Lead I	13 29%	13 52%	17 63%	28 74%	71
Lead aVL	4 9%	7 28%	10 37%	22 58%	43
Precordial leads	13 29%	12 48%	13 48%	24 63%	62
T waves					
Lead I	5 11%	9 36%	13 48%	21 55%	48
Lead aVL	3 7%	8 32%	12 44%	12 34%	35
Precordial leads	7 16%	10 40%	12 44%	17 45%	46
Intrinsicoid deflection	3 7%	0 0%	2 7%	5 13%	10

group and also yielded 15 (23.9 per cent) of the 63 false positive responses in the NH group. These T-wave abnormalities occurred with the same frequency in the extremity and chest leads.

VENTRICULAR ACTIVATION TIME. The ventricular activation time did not equal or exceed 0.06 second in any of the NH hearts but values in excess of this figure occurred in only 10 of the 135 LVH group an incidence of 7.4 per cent.

Influence of digitalization and myocardial infarction on criteria for LVH (LVH group) Having evaluated the sensitivity and specificity of the electrocardiographic criteria in the two broad groups (LVH and NH) we then assessed the influence of associated digitalization and/or myocardial infarction (Table VIII). There were 45 cases of pure LVH (Table III) uncomplicated by digitalization or anatomic evidence of infarction. Of these 29 cases (64 per cent) failed to meet a single one of the 11 criteria. (Note in Table V that when the total LVH sample was tested including those cases of infarction and/or digitalization 39 per cent did not fulfill any of the criteria.) Among 27 cases of LVH that were digitalized only 26 per cent did not meet even one criterion whereas of 25 hearts with LVH and infarction 43 per cent failed to meet at least one criterion. The association of LVH with digitalis effect and infarction (38 cases) resulted in one or more criteria being met in 87 per cent of the cases.

Influence of digitalization and myocardial infarction on criteria for LVH (NH group) When digitalized and infarcted hearts were removed from the 71 cases in the NH group 49 uncomplicated nonhyper trophied hearts remained Of these only 13 per cent yielded false positive responses to one or more criteria (Table VIII) as compared to a false-positive incidence of 29 per cent in the NH group when digital ized and infarcted cases were not removed (Table V) Among 9 NH hearts with ana tomic evidence of infarction 5 (55 per cent) satisfied at least one of the criteria of LVH There were 12 patients in the NH group who had been digitalized. Of these, 9 (75 per cent) met at least one criterion. The single nonhypertrophied heart which was both infarcted and digitalized satisfied 2 of the criteria for LVH

Influence of digitalis and infarction on individual criteria (LVH group) Those cases of infarction and or history of digitalization in the LVH group were further analyzed to determine which among the 11 component criteria were most responsible for the increased sensitivity and decreased specificity of response observed in the presence of these two complications.

QRS VOLTAGE. In each electrocardiogram there are 4 voltage criteria which may ideally be satisfied i.e. $R_1 + S_3 > 25$ $R_{AVL} > 11$ mm $S_{V1} + R_{V5} > 35$ mm $R_{V6} > 26$ mm. As shown in Table IXA among the 45 cases of pure LVH abnormal voltage was present in 21 of 180 possible instances, an incidence of 11.6 per cent when infarction alone complicated LVH (25 cases) voltage was abnormal 12 times (12 per cent incidence) digitalization was associated with 18 responses (16 7 per cent) of increased voltage among 27 cases digitalization and infarction together resulted in 19 instances (12.5 per cent) of abnormal voltage in 38 cases. Thus, voltage criteria alone are not appreciably influenced by digitalization and infarction.

RS-T DEPRESSION There are 5 individual criteria of RS-T segment depression i.e. in Leads I aVL V4 V5 and V6. Table IXA shows that whereas in 45 cases of pure LVH the RS-T segment was depressed 30 times (13.3 per cent) out of a possible 225 when infarction was also present (25 cases) there were 32 instances (25 6 per cent) of RS-T depression. Digitalization and LVH resulted in 40 (29 6 per cent) abnormal RS-T responses in 27 cases. Digitalis and infarction superimposed in 38 hearts with LVH produced 74 instances (38.9 per cent) of RS-T depression. Thus

Table IXB The influence of digitalization and myocardial infarction on individual component criteria in each of the clinical subtypes (NH)

Criteria	Clinical types (NH)				Total number cases
	Uncomplicated	Infarction	Digitalization	Infarction and digitalization	
Total	49	9	12	1	71
Voltage	1				1
		1	1		2
	1		1		2
	1	1	1		3
RS-T segments	2	5	8	1	16
	3	3	6		12
	1	4	7		12
T waves	1	2	2	1	6
		2	3		5
		2	2		4
					0

Table X. Heart weight in excess of normal in cases of LVH

Clinical type	Weight (Gm.) in excess of upper limit of normal
Uncomplicated	117 6
Infarction	113 0
Digitalization	152 7
Digitalization and infarction	185 7

the incidence of depression of the RS-T segment was significantly increased when digitalization and/or myocardial infarction coexisted with LVH

T WAVES T waves responded in much the same manner as did the RS-T segments the incidence of abnormality increased sharply as digitalization and/or infarction complicated the underlying LVH (Table IXA)

VENTRICULAR ACTIVATION TIME. Ventricular activation time like voltage was essentially uninfluenced by infarction and digitalization (Table IXA)

Influence of digitalis and infarction on residual criteria (NH group) Electrocardiograms of nonhypertrophied hearts were modified in association with digitalization and infarction to approximately the same extent as were those of hearts with LVH (Table IXB)

QRS VOLTAGE There were 3 instances of excessive QRS voltage among the 49 uncomplicated NH hearts 2 instances when infarction alone was present 3 with digitalization alone and none in the single case of digitalization combined with infarction Thus QRS voltage is not significantly influenced by digitalization and/or infarction in the NH group.

RS-T DEPRESSION RS-T-segment depressions increased in number in NH hearts complicated by digitalization and infarction For example there were 6 instances of RS-T depression among the 49 "pure NH hearts, 12 RS-T depressions in 9 hearts with infarction 21 depressions in 12 digitalized hearts, and the single NH heart with digitalization and infarction showed RS-T depression in Lead I

T WAVES. Among the 49 pure" NH hearts the T waves were abnormal in one instance but in the 9 cases with infarction there were 6 instances of T wave changes. In the 12 digitalized cases there were 7 abnormal T wave responses Again the single case with digitalis and infarction showed an inverted T wave in Lead I

Relation of digitalization and/or myocardial infarction to heart weight. In order to determine whether the decreased specificity and increased sensitivity of the electrocardiographic criteria observed in association with digitalization and infarction is due to a correlated variable namely the greater likelihood that patients who have had infarctions and/or who were digitalized have heavier hearts the mean heart weights in excess of normal[8] for the five subdivisions of LVH were calculated (Table X) Hearts with uncomplicated LVH averaged 117 6 grams above the upper limit of normal hearts with infarction were 113 0 grams above normal hearts of digitalized patients without infarction were 152 7 grams in excess of the upper limit of normal hearts with both infarction and digitalis were 185 7 grams above the normal limits. Thus increasing heart weight is a possible source of the altered electrocardiographic response in digitalized hearts with and without infarction among hearts with LVH However in the NH group, in which all heart weights were normal and in which the increasing weight cannot be responsible digitalis and infarction had the same effect on the electrocardiogram

Reliability of the teleoroentgenogram in the detection of LVH (Table XI) Among the 135 cases of LVH routine chest films had been recorded in 110 Cardiac size and contour were described as being within normal limits in 54 cases (49 per cent) and compatible with LVH in the other 56 (51 per cent)

Among the 71 NH hearts, x-ray films of the chest had been obtained in 62 Of these 54 (87 per cent) were described as showing no roentgenologic evidence of LVH or cardiomegaly However there were 8 cases (13 per cent) in which the teleoroentgenogram was interpreted as indicating LVH (e.g cardiothoracic ratio greater than 0.50 left ventricular border elongated or prominent) Among these 8 cases which were false positives by x-ray

Table XI Reliability of x ray diagnosis of LVH

X-ray diagnosis	Autopsy findings			
	LVH		NH	
	Number	Per cent	Number	Per cent
LVH	54	49	8	13
NH	56	51	54	87
Total	110	100	62	100

examination the electrocardiogram was also indicative of LVH (by voltage criteria) in one was normal in 6 others, and showed low voltage in the remaining case.

Discussion

Results obtained from this correlation of the anatomic and electrocardiographic findings in 135 hearts with left ventricular hypertrophy and 71 nonhypertrophied hearts indicate that the currently used electrocardiographic criteria of LVH are, for the most part, inadequate. Thus, among all hearts with hypertrophy of the left ventricle, 39 per cent failed to satisfy a single electrocardiographic criterion. Of equal significance is the observation that 29 per cent of the cases without autopsy evidence of LVH did fulfill one or more of these criteria. The most satisfactory results were obtained when one required that at least any 3 of the 11 criteria listed by Sokolow and Lyon (Table IV) be met before the diagnosis of LVH was permissible—with 45 per cent of the hypertrophied hearts correctly identified and 11 per cent of the nonhypertrophied hearts still falsely labeled as LVH Any attempt to liberalize this required number of criteria so as to increase the incidence of hearts with LVH correctly identified resulted in more of the control cases being erroneously designated as hypertrophied.

Analysis of the sensitivity and specificity of the various criteria indicated that among the nonhypertrophied hearts the greatest number of false-positive responses were due to RS-T-segment depressions which accounted for 40 of the 63 individual abnormalities found in this group. Abnormal T waves occurred less commonly than did RS-T-segment deviations (23 9 per cent of the total number of positive responses) Abnormally high voltage of QRS occurred in only 8 of the 63 false positive instances (12.7 per cent) Ventricular activation time never exceeded the upper limit of normal, 0 05 second in the absence of hypertrophy of the left ventricle.

The depressed RS-T-segment in addition to being the least specific of the criteria was, however most sensitive to the presence of LVH scoring 45.5 per cent of the total number of correct positive responses. T wave changes were slightly less sensitive than were the RS-T-segments, giving 36 per cent of the correct responses in the LVH group with a specificity of 76 per cent.

The following voltage criteria of QRS were highly specific, although relatively insensitive, accounting for only 18 per cent of the total number of correct electrocardiographic responses (a) $R_1 + S_3 = > 25$ mm. (b) $S_{V1} + R_{V5}$ (V_6) > 35 mm. (c) $R_{AVL} = > 11$ mm.

The criterion of prolongation of ventricular activation time beyond 0.05 second in the left precordial leads was met in only 7 4 per cent of all cases of LVH so low an incidence as to detract seriously from its usefulness as an important electrocardiographic sign of LVH

This study further indicates that associated digitalization and/or myocardial infarction greatly influence the electrocardiographic recognition of LVH by depressing RS-T segments and lowering or inverting T waves. Thus, when the sample was purified so as to separate hearts with these latter complications, 64 per cent of the remaining 45 cases of "pure" LVH revealed no electrocardiographic abnormality whatsoever i.e. they failed to meet a single criterion of LVH Of 49 "pure NH hearts, 13 per cent met one or more of the criteria of LVH In contrast in hearts with LVH and infarction one or more criteria were met in 57 per cent of cases, in 74 per cent of cases with LVH and digitalization and in 87 per cent of hearts with LVH [illegible] d digitalis.

In the NH group complicated by infarction alone 55 per cent met at least one criterion of LVH in those complicated by digitalization alone 75 per cent satisfied one or more criteria There was only one nonhypertrophied heart which showed evidence of infarction and had also been digitalized and although this also met more than one criterion no conclusion is permissible from this single case

The criteria most profoundly influenced by the presence of digitalization and infarction in both the LVH and NH groups were those dealing with RS-T-segment depression and T wave alterations. QRS amplitude and ventricular activation time retained their specificity (albeit with limited sensitivity) to LVH despite the addition of these complications

The effect of digitalis but not of myocardial infarction on the RS-T-segments and T waves in hearts with LVH may be associated with the correlated variable of increasing heart weight since in the LVH group hearts with these complications weighed significantly more than did the hearts of the pure group. However the fact that increased QRS voltage was found to be the most specific electrocardiographic evidence of LVH and that its incidence did not increase correspondingly suggests that the changes in response of the RS-T segments and T waves are not primarily a function of increasing cardiac mass. The occurrence of an identical response to digitalis and infarction in the nonhypertrophied hearts in which increasing weight is not a factor further supports this conclusion

It is difficult to reconcile these results with those of Scott[1] in whose experience 85 per cent of the cases with LVH were correctly identified with the electrocardiogram when the same criteria employed here were used

The criteria used most widely for the electrocardiographic recognition of left ventricular hypertrophy include the following (a) increased amplitude of QRS complexes (b) RS-T depressions and T wave lowering or inversion usually maximal in those leads in which the R wave is of greatest amplitude and (c) prolonged ventricular activation time in the left precordial leads

The mechanism for the production of high-voltage QRS complexes in LVH has been attributed to several factors. These include (a) greater magnitude of the cardiac vectors produced during epicardial excitation due to the greater epicardial surface area of the hypertrophied left ventricle[8,9] (b) greater proximity of the free wall of the hypertrophied left ventricle to the chest wall[10-12] resulting in greater potential recorded and (c) increased voltage on excitation generated by the individual hypertrophied muscle fibers[13,14]

Abnormalities of the RS-T segment and T waves are believed to occur in LVH because of changes in the direction of repolarization as well as alterations in the time relationships between repolarization and depolarization[15] Thus, presumably because of thicker chamber walls repolarization begins to take place in the subendocardial region before the wave of depolarization has arrived at the epicardial area. However the possibility that such RS-T segment and T wave changes observed in the tracings of patients with LVH are manifestations of primary myocardial disease rather than of simple chamber enlargement cannot be excluded[12,13]

Prolongation of ventricular activation time probably results from the wave of excitation having to traverse an increased thickness of the left ventricular wall

The renewed observation that RS-T segment depressions and T wave changes are highly nonspecific indicators which should be interpreted with caution when left ventricular hypertrophy is being evaluated electrocardiographically deserves emphasis in view of their inclusion in almost all sets of criteria of LVH Although frequently present in tracings from hypertrophied hearts these changes also occur in the absence of hypertrophy especially in response to myocardial ischemia necrosis and digitalis. There are many other important and frequent causes of RS-T segment depression and T wave changes. These include electrolyte imbalance hyperventilation autonomic imbalance in nervous or psychotic individuals, altered physiologic states changes in respiration and myocarditis. Kossmann[16] would appear to be correct in his conclusion that RS-T-segment and T wave changes alone

may not be interpreted as necessarily reflecting any anatomic alteration.

Whatever the mechanisms proposed for the production of high-voltage QRS complexes, it is clear that they are operative in only a minority of cases of LVH and occur infrequently in the absence of anatomic evidence of LVH. Such variable factors as thickness of the chest wall, anatomic position of the heart within the thoracic cage and its relation to the overlying chest electrodes, force of myocardial contraction and pleural, pulmonary, and pericardial disease—all fundamentally unrelated to the size of the left ventricle—can and do influence QRS voltage. Furthermore, the development of ventricular dilatation in a hypertrophied chamber may also alter the QRS voltage.

The absence of false-positive prolongation of ventricular activation time in this study does not rule out the possibility that this time interval may be prolonged under circumstances other than LVH, as for example in intraventricular conduction defects or diffuse myocardial fibrosis (both of which slow passage of the wave of excitation through the heart). Its low incidence among hearts with LVH deserves emphasis.

Routine roentgenologic examination of the chest in the posteroanterior view is somewhat less reliable than is the electrocardiogram in the recognition of LVH. Thus, about half the cases with LVH are not diagnosed by this technique. There is the additional consideration of convenience and practicality, since it is much less difficult to record an electrocardiogram than a teleoroentgenogram, especially in moribund patients. The incidence of false-positive indications of LVH by x-ray examination was 13 per cent, somewhat higher than the false-positive results obtained from the electrocardiogram when voltage criteria alone are considered.

Conclusions

Certain conclusions may be drawn from the data obtained in this study. The electrocardiogram is more reliable than the routine teleoroentgenogram in the recognition of LVH. The only reasonably sensitive and specific electrocardiographic criteria for the detection of LVH appear to be increased voltage in Leads I and III, aVL, V_1, V_5 (or V_6), and prolongation of the ventricular activation time in the left precordial leads. Consideration of the RS-T segments and T waves in the absence of such increased voltage or prolonged duration of intrinsicoid deflection is unreliable because of the nonspecificity of these changes. There is no need to demand that RS-T segments and T wave changes be present, in addition to increased voltage, in order to make the diagnosis of LVH, since these former abnormalities may indicate processes other than ventricular hypertrophy and do not increase the sensitivity of the voltage criteria. The voltage criteria in the limb and chest leads are of equal sensitivity and specificity, so that if any one set is met, the likelihood of LVH is high. The presence of digitalization and/or myocardial infarction in a given patient makes it mandatory that RS-T segment and T wave changes be disregarded, since these complications result in a very high incidence of false-positive results. They do not, however, appear to have any effect on QRS voltage.

A normal electrocardiogram and/or teleoroentgenogram by no means rule out the presence of LVH, nor does the abnormal voltage of QRS (with or without accompanying RS-T and T-wave changes) always necessarily indicate such enlargement.

Summary

This study correlated the cardiac findings at autopsy with electrocardiograms and teleoroentgenograms of 135 patients with left ventricular hypertrophy. Tracings and chest x-ray films from 71 patients without anatomic evidence of cardiac hypertrophy served as a control group. The reliability of the chest film as well as the sensitivity and specificity of the set of 11 electrocardiographic criteria for LVH enumerated by Sokolow and Lyon were evaluated and compared. Reasons for selecting these criteria are discussed. The electrocardiogram is generally a more adequate means for the detection of LVH than is the chest x-ray film. The more sensitive but least specific indicators of LVH appear to be RS-T-segment depres-

sion and T wave abnormalities. These are also the criteria most influenced by the presence of digitalization and infarction. Increased amplitude of QRS is more specific and much less sensitive an indicator of LVH and does not appear to be influenced by associated digitalization or infarction. The most specific criterion of LVH is prolongation of the ventricular activation time but it is so insensitive as to be of limited value.

Possible mechanisms for the genesis of the electrocardiographic changes in left ventricular hypertrophy are discussed.

REFERENCES

1. Scott, R. C. The correlation between the electrocardiographic patterns of ventricular hypertrophy and the anatomic findings, Circulation 21:256, 1960.
2. Dimond, E. G. Electrocardiography, St. Louis, 1954, The C. V. Mosby Company.
3. Burch, G. E., Horan, L. G., Ziskind, J., and Cronvich, J. A. A correlative study of post-mortem electrocardiographic and spatial vectorcardiographic data in myocardial infarction, Circulation 18:325, 1958.
4. Allenstein, B. J., and Mori, H. Evaluation of electrocardiographic diagnosis of ventricular hypertrophy based on autopsy comparison, Circulation 21:401, 1960.
5. Scott, R. C., Seiwert, V. J., Simon, D. L., and McGuire, J. Left ventricular hypertrophy: a study of the accuracy of current electrocardiographic criteria when compared with autopsy findings in one hundred cases, Circulation 11:89, 1955.
6. Zeek, P. M. Heart weight. I. The weight of the normal human heart, Arch. Path. 34:820, 1942.
7. Sokolow, M., and Lyon, T. P. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads, Am. Heart J. 37:161, 1949.
8. Grant, R. P. The relationship between the anatomic position of the heart and the electrocardiogram. A criticism of "unipolar" electrocardiography, Circulation 7:890, 1953.
9. Grant, R. P. Clinical electrocardiography: the spatial vector approach, New York, 1957, McGraw-Hill Book Company, Inc.
10. Sodi-Pallares, D. New bases of electrocardiography, St. Louis, 1956, The C. V. Mosby Company.
11. Lepeschkin, E. Modern electrocardiography. Vol. I. The P-Q-R-S-T-U complex, Baltimore, 1951, The Williams & Wilkins Company.
12. Barker, J. M. The unipolar electrocardiogram. A clinical interpretation, New York, 1952, Appleton-Century-Crofts Company, Inc.
13. Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D. Interpretation of ventricular complex of electrocardiogram, Advances Int. Med. 2:1, 1947.
14. Lipman, B. S., and Massie, E. Clinical unipolar electrocardiography, ed. 3, Chicago, 1956, Year Book Publishers, Inc.
15. Kossmann, C. E. Advances in electrocardiography, New York, 1958, Grune & Stratton, Inc.

Embolism to the right side of the heart

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Emboli from the systemic veins rarely terminate in the chambers of the right side of the heart in man. The majority of emboli pass through these chambers to various parts of the pulmonary arterial system. However a few cases have been reported in which large coiled emboli have obstructed the outflow tract of the right ventricle and caused sudden death [1,2] There has been an occasional instance in which large emboli have "lodged" in the tricuspid orifice again resulting in obstruction and sudden death.[3] Blumer [3] Belt [4] and Hollister[5] have mentioned emboli trapped in the chordae tendineae of the tricuspid valve but in none of these reports was death attributed specifically to this finding In addition emboli trapped in anomalies of the venous valves of the right atrium (including Chiari's network)[6,7] have been reported

In the case which we now report, necropsy revealed an embolus entangled in the chordae tendineae of the tricuspid valve this caused sufficient obstruction of that orifice to account for sudden death.

Case report

F J a 74-year-old white widow was admitted to the University of Oklahoma Hospitals for the first and only time on March 5 1960. Her chief complaint on admission concerned gas pains crowding her heart these had been present for about 12 hours. She had had high blood pressure and "heart trouble" for several years. The latter consisted of infrequent dull substernal pains which did not radiate, intermittent edema of the feet and ankles, and some shortness of breath on exertion. There was no history which suggested previous phlebitis or embolic phenomenon.

The physical examination at the time she was admitted to the hospital revealed a moderately obese elderly white woman who had slight dyspnea at rest. The blood pressure was 200/100 mm. Hg, the pulse was 80 per minute and regular the respirations were 16 per minute, and the temperature was 97 8°F The cardiac point of maximum impulse was located 1.5 cm. to the left of the mid-clavicular line in the fifth intercostal space. The pulmonic second sound was greater than the aortic second sound There was a Grade I soft apical systolic murmur There were a few inspiratory râles at both lung bases posteriorly The edge of the liver was firm and slightly tender located 4 cm. below the right costal margin. Moderate pitting edema of the ankles was noted. The lower legs were tender to pressure, but Homans sign was not elicited. The remainder of the examination was not remarkable.

On admission, the hemoglobin was 14 0 Gm per 100 ml. the white blood cell count was 9,200 with 78 per cent neutrophils. Urinalysis gave a one-plus test for protein the sediment contained 3 to 5 white cells and no red cells per high-power field. The SGO-T was 210 and the SGP T was 74 units 36 hours after admission, but fell to normal values by the fifth hospital day The serum cholesterol was

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Fig. 1. *Top.* Photomicrograph of the central part of the thromboembolus at low magnification (hematoxylin and eosin stain, ×23). *Bottom.* Same as above but at higher magnification (×500) (see text).

208 mg. per cent. Serum electrolytes obtained 2 hours before death were sodium 140, chloride 91, potassium 4.8, and carbon dioxide 30.6 mEq. per liter. Serial electrocardiograms showed an extensive acute anteroseptal and anterolateral myocardial infarction.

On admission the patient was placed on strict bed rest. Oral digitalization and anticoagulation with heparin and warfarin sodium were started. During the first 24 hours, the patient sustained a moderate diuresis, and the pains in her chest lessened. Heparin was discontinued on the second hospital day. By the fourth hospital day her blood pressure had dropped to a range of 110-124/60-65 mm. Hg. She was maintained on digoxin 0.25 to 0.5 mg. per day by mouth and was given chlorothiazide 0.5 Gm. per day for the remainder of the hospitalization. A pericardial friction rub developed on the sixth hospital day and warfarin was discontinued for 3 days. Subsequently prothrombin times ranged from 19 to 52 seconds, but during the last week of her life they were maintained between 24 and 33 seconds.

From the time of admission the patient complained that her legs hurt, especially the right leg. On the twenty-seventh hospital day her main complaint concerned pain in the lower legs, which still were edematous, warm, and markedly tender to the touch. Throughout the hospitalization a positive Homans sign was not recorded.

On the twenty-eighth hospital day she was checked routinely at 8:00 A.M. and the blood pressure was recorded as 100/68 mm. Hg and the pulse was 80 per minute. At approximately 8:45 A.M., while being assisted to a bedside commode she experienced the sudden onset of upper abdominal pain, weakness, and breathlessness. Heart sounds were described as "regular and strong," although no pulse or blood pressure were obtainable. She became unresponsive and developed gasping respirations. She was pronounced dead at 8:50 A.M.

The necropsy was performed 9 hours after death. The heart weighed 380 grams. On gross inspection there was an extensive anteroseptal myocardial infarction with some associated localized fibrinous pericarditis. Inspection of the right side of the heart revealed a firm, dark red embolus entangled in the chordae tendineae of the anterior and medial (septal) cusps of the tricuspid valve, drawing these two cusps tightly together in the position of valve closure. This had produced approximately 80 per cent obstruction of the tricuspid orifice. The posterior cusp, which was small in this heart, remained relatively free. A part of the embolus extended along the base of the anterior wall of the right ventricle, part way into the pulmonary cone. The total length of the embolus was 4.5 cm. In the lateral wall of the right atrium was an oval-shaped aneurysmal dilatation which measured 3.5 cm. in greatest diameter. The right ventricle was slightly hypertrophied but not dilated.

The left anterior descending coronary artery was 80 per cent occluded by atheromata. The remainder of the coronary arteries disclosed slight to moderate arteriosclerosis. The heart valves, including the tricuspid valve, revealed only minimal sclerosis.

Numerous microscopic sections failed to reveal any attachments of the thromboembolus to the endocardium. The oldest portion of the clot showed irregular partially laminated structure (Fig. 1, *top*) and appeared microscopically to be 2 to 5 days old. The lower part of Fig. 1 shows part of the thin

*Coumadin, Endo Laboratories, Inc., Richmond Hill, N. J.

tenuous endothelium (*arrow*) which covered the thromboembolus, separating it from more recent thrombotic material.

Microscopically the anteroseptal myocardial infarction appeared to correspond in age with the clinical interval of 4 weeks. A small mural thrombus in the left ventricle was attached to the infarcted surface. Microscopically this thrombus appeared to be about 10 days old. No other mural thrombi were found in the heart. In the area of the localized dilatation of the right atrial wall, microscopic examination showed marked widening of the spaces between the musculae pectinati and some scattered fibrosis in the atrial muscle.

No emboli were demonstrated in the pulmonary arteries, with the exception of a single microscopic, unattached embolic fragment in a small peribronchial artery. Whether this fragment originated in a systemic vein or the left ventricle could not be determined. The remainder of the autopsy, including examination of the brain, revealed moderate generalized arteriosclerosis, slight obstructive emphysema, chronic cholecystitis and cholelithiasis, chronic pyelonephritis, and moderate congestion of the liver. The leg veins were not examined.

Discussion

The clinical impression was that this 74-year-old woman had died suddenly of pulmonary embolism 4 weeks after an acute myocardial infarction. There had been presumptive clinical evidence of thrombophlebitis of the lower extremities, and this was postulated as the source of embolization. None of the clinical findings distinguished this sudden death from that seen in those patients who die immediately from pulmonary embolism. Even when it is considered to be satisfactory, anticoagulation is not, by any means, complete insurance against embolization.[5-9]

At necropsy no pulmonary embolus was visible grossly and the peculiar embolus described above was almost disregarded as postmortem clot material. However, this recently formed thromboembolus had apparently become trapped in the chordae tendineae of the anterior and medial (septal) leaflets of the tricuspid valve during its passage through the right ventricle. This sudden obstruction to most of the blood flow through the tricuspid orifice appears to be an adequate explanation for the sudden death. On the basis of the clinical and pathologic information available, the original source of the embolus was probably a propagating thrombus in a leg vein.

The lack of any attachment to the endocardium differentiates this clot from a mural thrombus. There were no true attachments to the chordae tendineae either to suggest primary intracardiac formation. Certainly this type of obstruction of the atrioventricular orifice differs from that described in cases of "mass" thrombi (including ball thrombi).[11,17]

It is quite possible that some emboli to the right side of the heart have been overlooked in our modern era of medicine when the doctrine of death from "heart-clot" is passé.[18] Thus, to a careful method of examination for pulmonary embolism we would add and re-emphasize scrutiny of intracardiac clot material in cases of sudden death.

Summary

The sudden death of a 74-year-old woman who was recovering from a myocardial infarction is attributed to an unusual result of thromboembolism. The embolus, by a curious twist of fate, had become trapped in the chordae tendineae of the tricuspid valve and produced a major obstruction to blood flow through the tricuspid orifice.

We would like to thank G. Kenneth Mallory, M.D., Mallory Institute of Pathology, Boston City Hospital, and Ira Gore, M.D., Chief of Pathology, West Roxbury Veterans Hospital, for reviewing microscopic sections from this case.

REFERENCES

1. Adami, J. G., and Nicholls, A. G.: The principles of pathology, Vol. II, New York, 1909, Lea & Febiger, pp. 48-54.
2. Wartman, W. B., and Hellerstein, H. K.: The incidence of heart disease in 2,000 consecutive autopsies, Ann. Int. Med. 28:41, 1948.
3. Blumer, G.: Thrombosis, embolism and phlebitis. *In* Osler, W., editor: Modern medicine, its theory and practice, Vol. IV, Philadelphia, 1908, Lea & Febiger, pp. 539-560.
4. Belt, T. H.: Pulmonary embolism, Canad. M.A.J. 30:253, 1934.
5. Hollister, L. E., and Cull, V. L.: The syndrome of chronic thrombosis of the major pulmonary arteries, Am. J. Med. 21:312, 1956.
6. Yater, W. M.: Variations and anomalies of the venous valves of the right atrium of the human heart, Arch. Path. 7:418, 1929.
7. Hackensellner von H. A., and Schmidt, K.: Seltene anatomische Ursache eines Falles von Akutem Budd-Chiari schen Syndrom, Cardiologia 31:162, 1957.
8. Byrne, J. J., and O'Neil, E. E.: Fatal pulmonary emboli. A study of 130 autopsy-proven fatal emboli, Am. J. Surg. 83:47, 1952.
9. Byrne, J. J.: Phlebitis. A study of 748 cases at



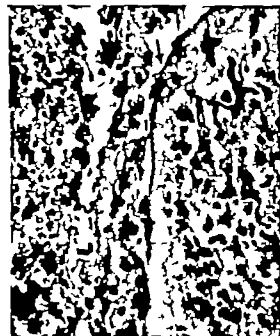


Fig. 1. *Top.* Photomicrograph of the central part of the thromboembolus at low magnification (hematoxylin and eosin stain, ×23). *Bottom.* Same as above but at higher magnification (×500) (see text).

208 mg. per cent. Serum electrolytes obtained 2 hours before death were: sodium 140, chloride 91, potassium 4.0, and carbon dioxide 30.6 mEq. per liter. Serial electrocardiograms showed an extensive acute anteroseptal and anterolateral myocardial infarction.

On admission the patient was placed on strict bed rest. Oral digitalization and anticoagulation with heparin and warfarin sodium* were started. During the first 24 hours, the patient sustained a moderate diuresis, and the pains in her chest lessened. Heparin was discontinued on the second hospital day. By the fourth hospital day her blood pressure had dropped to a range of 110-124/60-65 mm. Hg. She was maintained on digoxin, 0.25 to 0.5 mg. per day by mouth, and was given chlorothiazide, 0.5 Gm. per day, for the remainder of the hospitalization. A pericardial friction rub developed on the sixth hospital day, and warfarin was discontinued for 3 days. Subsequently, prothrombin times ranged from 19 to 52 seconds, but during the last week of her life they were maintained between 24 and 33 seconds.

From the time of admission the patient complained that her legs hurt, especially the right leg. On the twenty-seventh hospital day her main complaint concerned pain in the lower legs, which still were edematous, warm, and markedly tender to the touch. Throughout the hospitalization, a positive Homans sign was not recorded.

On the twenty-eighth hospital day she was checked routinely at 8:00 A.M., and the blood pressure was recorded as 100/68 mm. Hg and the pulse was 80 per minute. At approximately 8:45 A.M. while being assisted to a bedside commode, she experienced the sudden onset of upper abdominal pain, weakness, and breathlessness. Heart sounds were described as "regular and strong," although no pulse or blood pressure were obtainable. She became unresponsive and developed gasping respirations. She was pronounced dead at 8:50 A.M.

The necropsy was performed 9 hours after death. The heart weighed 380 grams. On gross inspection there was an extensive anteroseptal myocardial infarction with some associated localized fibrinous pericarditis. Inspection of the right side of the heart revealed a firm, dark red embolus entangled in the chordae tendineae of the anterior and medial (septal) cusps of the tricuspid valve, drawing these two cusps tightly together in the position of valve closure. This had produced approximately 80 per cent obstruction of the tricuspid orifice. The posterior cusp, which was small in this heart, remained relatively free. A part of the embolus extended along the base of the anterior wall of the right ventricle, part way into the pulmonary cone. The total length of the embolus was 4.5 cm. In the lateral wall of the right atrium was an oval-shaped aneurysmal dilatation which measured 3.5 cm. in greatest diameter. The right ventricle was slightly hypertrophied but not dilated.

The left anterior descending coronary artery was 80 per cent occluded by atheromata. The remainder of the coronary arteries disclosed slight to moderate arteriosclerosis. The heart valves, including the tricuspid valve, revealed only minimal sclerosis.

Numerous microscopic sections failed to reveal any attachments of the thromboembolus to the endocardium. The oldest portion of the clot showed irregular, partially laminated structure (Fig. 1, *top*) and appeared microscopically to be 2 to 5 days old. The lower part of Fig. 1 shows part of the thin

*As Coumadin, Endo Laboratories, Inc., Richmond Hill, N. J.

The normal Q-T interval

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The Q-T interval is an important diagnostic criterion in clinical electrocardiography, and there is abundant literature concerning its changes in various pathologic conditions. Although a pronounced prolongation of the Q-T interval can be easily recognized, moderate or small deviations from the normal limits predicted from the heart rate are subject to considerable error. The relationship between the heart rate (or its reciprocal value, the R-R interval) and the Q-T interval shows considerable variation, and, therefore, a wide scatter. It is not surprising that various formulas[1-3] (square root, cubic root, logarithmic, linear) have been proposed for the prediction of the Q-T interval from the heart rate; these are summarized in Table I. The square root formula of Bazett[1] is used most frequently in North America, and the cube root formula of Fridericia in Europe. Some formulas are quite similar, for instance, those of Bazett,[1] and Shipley and Halloran.[3] A comparatively small deviation of the Q-T interval of an individual patient may fall within the normal limits of one of the equations and exceed those of another.

On the other hand, in view of the wide scatter of the Q-T versus the R-R interval two or more equations may fit equally well in the same sample, or in different samples different equations may give the better fit. This is, of course, the reason that various authors suggest different formulas. It is probable that the difference in equations is largely due to chance variations in sampling, or to a different composition of the samples. For an adequate statistical evaluation, the size of the sample should be large, a factor which was not met in the original communications of Bazett and Fridericia. However, a large sample size alone does not guarantee reliability of prediction, for the composition of the sample is equally important. The sample should be representative of an average, healthy population; samples which include "cardiovascular normal" patients, i.e., patients with other than cardiovascular disease, do not fulfill this requirement. Unfortunately, information about the composition of samples is not complete, but most include "cardiovascular normal" patients. The healthy soldiers in the sample of Schlamowitz[4] were preselected as to physical fitness, and therefore, are not representative of the average "healthy" population. Difference in the composition of the sample is not the only factor which may be responsible for the

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Table I Suggested formulas for relationship between R R and Q-T intervals

Authors	Size and composition of group	Lead	Formula	
Barett (1920)	M 20 F 19 Normal subjects	II	$k\sqrt{RR}$	M k = 0.368 (range 0.342 to 0.392) F: k = 0.399
Shipley and Halloran[2] (1936)	M and F 200. Normal subjects. Age 22 to 35 yr	II	$k\sqrt{RR}$	M k = 0.397 F k = 0.415
Hegglin and Holzmann[3] (1937)	M and F: 700. Normal subjects and patients without heart disease	II	$k\sqrt{RR \pm 0.04}$	k = 0.39 (for M and F) Good for R R 0.40 to 1.50
Fridericia[4] (1920)	M and F 50 Normal subjects. Age 30 to 81 yr	II	$k\sqrt[3]{100\,RR}$	k = 0.0822
Schlomka and Raab[5] (1936)	M and F 336. Subjects without heart disease	II	$k\sqrt[3]{100\,RR}$	(Age) 20 to 30 k = 0 0795 40 to 50 k = 0 0802 60 to 70 k = 0.0815 Over 70 k = 0.0826
Ashman[6] (1939)	M: 432. F 425 Children 200 Subjects without heart disease	II	$K \log(10[RR + K_4])$	Young M K = 0.373 Young F: K = 0.385 Elderly M K = 0.380 Elderly F K = 0.390 Children K = 0 376 For all groups K = 0 07
hman and Hull[7] (1945)	2 000 cases		$K \log(10[RR + K_4])$	Revised constants Young F K = 0.385 Elderly M: K = 0.380 Elderly F: K = 0.385 Children K = 0 375 For all groups K_4 = 0.07
Schlamowitz[8] (1946)	M 650. Healthy soldiers. Age 18 to 44 yr	II	0.205 R R + 0.167	
Mayeda (1934)	M 135 F 65. Normal subjects and patients without heart disease Age 18 to 64 yr Heart rate 54.5 to 115.8	II	$(M[100\,RR])^N$	M=0.2574 N=0.604

R-R interval measured in seconds.
F Female. M Male.

large variation in the relationship between heart rate and Q-T interval The considerable error in measurement of the Q-T interval[10] contributes importantly to this variability

A change in heart rate even before the electrocardiogram is recorded may affect the relationship between the heart rate and the Q-T interval since adaptation of the Q T interval to the heart rate is slow and may extend over several weeks in certain conditions, as in semistarvation.[11]

The purposes of this study were (1) to attempt to reduce the wide scatter in the relationship between heart rate and Q-T interval by consideration of constitutional factors such as age relative body weight sex, and blood pressure and of electrocardiographic characteristics such as QRS and T amplitudes and axes, in order to

improve the correlation between the Q-T and the R R intervals and other factors and (2) to determine the best obtainable fit and reliable upper and lower limits of normal for the Q-T interval dependent upon heart rate and other factors in a carefully selected large sample (960 adult men and women) which is suggested to be representative of the average, healthy adult population of the United States.

Sample

Electrocardiograms of 649 men and 311 women who ranged in age from 20 through 59 years were analyzed. Most of the men were from a randomly selected sample of over 3,000 railroad employees working in the midwestern and northwestern United States.* They were supplemented in the age group from 20 to 29 years by male employees of the Mutual Service Insurance Companies,† St. Paul Minnesota. The female subjects were employees of Mt Sinai Hospital‡ and Asbury Methodist Hospital § of Minneapolis Minnesota the [M]utual Service Insurance Companies† [St.] Paul Minnesota and the Provident [Mu]tual Life Insurance Company ‖ Phil[ade]lphia Pennsylvania. Healthy men and [wom]en were selected from a larger sample

~\\ square was a sta[...] crease of the [...] puted from [...] increase of th[...] to 90 beats [...] sample of 960

Table II show[...] interval predict[...] from different fe[...] means of men fron[...] arbitrarily selected [...] different Q-T and [...] group mean (first colu[...] for the average and th[...] are closer to the extre[...]

*[...] cardiologic study of the railroad population is under [dir]ection of Dr Henry L. Taylor.
†[...]plied by Dr Henry Blackburn, Medical Director
‡[...]ected by Dr P Eurenstadt, Dr. E. Maja, and Dr
§[...]d by Dr. James Dodd.
‖ by Dr Paul H Langner, Medical Director.

on the basis of medical history and physical examination Subjects with the following physical conditions which may affect the ECG were excluded blood pressure of or above 160 mm. Hg systolic or 95 mm. Hg diastolic clinical diagnosis of heart disease cardiac murmurs that were greater than Grade 2 in intensity chronic broncho-pulmonary disease renal disease diabetes mellitus thyroid disease peptic ulcer active gall-bladder disease and convalescence from recent infection

Method, measurement and evaluation

A 12 lead ECG was taken in the supine position after 15 minutes of rest P Q R, S and T deflections were measured according to criteria of the American Heart Association[12] in all 12 conventional leads P R R R, QRS, and Q-T intervals were measured in the limb leads. For evaluation the longest Q-T interval in any of the standard leads (usually Lead II) was used The analysis of regression equations was done by means of computers. In addition to R R and Q-T intervals, age sex height, absolute and relative body weight and blood pressure were included in the computer analysis. Relative body weight was determined from height-weight data for age from the standard medico-actuarial tables.[13] This is a rather crude measure but is sufficient for gross characterization of underweight normal weight and overweight. Of ECG characteristics, QRS and T frontal plane axes, R and T waves in Leads I II aV F

duration formulas of Cody Woodbury and Simonsen compared to other pub-

Subject	Group mean	A	B	C	D	E	F	G
Age	50	55	25	45	45	55	25	45
Q-T	38	43	37	43	34	41	36	37
R-R	88	1 18	84	1 14	64	79	78	80
Prediction equation								
Barett	34	40	34	39	30	36	36	
Shipley	37	43	36	42	32	37	37	
Schlomka	35	40	35	39	32	35	34	
Ashman	37	42	36	41	33	36	36	
Schlamowitz	34	41	34	40	31	33	33	
Mayeda	38	43	37	43	32	36	36	
CWS log	38	42	37	41	35	37	36	
CWS linear	38	42	37	42	35	37	36	

96
35 34
40 41
77
35 35
42 42
43
37 36
43 44
20
39 36
1 46 46

years show a slight difference. The discrepancies are larger at heart rates from 45 to 55 per minute but the samples are too small at that range of heart rates for reliable determination of normal limits. Therefore normal limits at heart rates 45 to 55 are preliminary

The results in Table IV show as a whole good agreement between the 2 5 and 97 5 actual percentile distribution and the prediction from the CWS(2) equation

Discussion

In spite of different formulas the differences in the upper limits of normal (Table III) are comparatively small. This might be because of the wide scatter of Q-T values versus heart rates. The sources for the scatter could not be defined in spite of the numerous factors considered in the computer analysis. Only age made a small but significant contribution Of course the random scatter determines to a greater degree the normal limits for any formula used Among the factors which are most likely important for the Q-T interval is the heart rate prior to the recording of the ECG possibly for veral hours or more This information s not available to us nor will it be ilable in epidemiologic studies or for mbulatory patients. Geppert[16] analyzed the relationship between the R R and Q-T intervals using a linear and an exponential formula on 600 occasions of different heart rates in one healthy individual The variation of the constants in both formulas was enormous.

The linear formula CWS(2) is based on a large sample carefully selected to be representative of an average healthy adult population of the United States. That none of the factors except age utilized in the computer analysis made an important contribution is perhaps, disappointing in our attempt to reduce the scatter but the resulting linear equation is very simple—in fact simpler than most of the other equations suggested In arbitrarily selected individual subjects with extremes of heart rate or Q-T interval it gave when compared with other equations, the most consistently closest agreement to the actual values. The good agreement with normal limits determined from the actual percentile distribution and from the CWS(2) formula is encouraging for recommendation of the CWS formula as the best obtainable expression for the relationship between the Q T interval and the heart rate. Table IV presents the analysis in a form convenient for clinical application. For heart rates from 56 to 115 per minute it makes little difference whether the values derived from the actual percentile distribution or from the CWS(2) formula are used It is suggested that the more extreme values be used in instances of slight differences. For Q-T intervals at heart rates from 45 to 55 per minute the values derived from the percentile distribution are recommended although they are tentative because of small sample size Extension of the prediction for tachycardia over 115 per minute is not possible this is true for other formulas also. Sinus tachycardia above 115 or bradycardia below 55 per minute in healthy adults is rare so that it is difficult to collect a sufficient number of subjects with these rates even in a large sample The prediction also cannot be applied to electrocardiograms with gross deformation of the QRS complex (bundle branch block ventricular rhythm)

Changes in the Q-T interval (usually based on Bazett's formula) have been used in exercise[17] and hypoxemia tests.[18] The rapid change in the heart rate and increased stroke volume in exercise precludes application of Bazett's formula or any other obtained from resting electrocardiograms. The true relationship between the Q-T and R R intervals in tachycardia during exercise is unknown and this can be determined only in a large series of subjects in the steady state of exercise (or hypoxemia) preferably extending over a period of 30 minutes to 1 hour The empirical utilization of the changes in the Q-T interval in these conditions is based on the rate of adaptation of the Q T interval to the heart rate This depends upon the heart rate before exercise the rate of increase during exercise and the rate of decrease during recovery

That differences in the rate of adaptation exist between patients with cardiac abnormalities and normal subjects is not doubted but the already great uncertainties of

prediction in the resting condition are multiplied in exercise.

Summary

1 The correlation between the Q-T and the R R intervals was determined in 649 healthy men and 311 healthy women from 20 to 59 years of age with consideration of constitutional and physiologic variables and ten additional electrocardiographic items using an electronic computer

2. Of the numerous factors investigated only age made a small, but statistically significant, contribution to the relationship between the Q-T and the R R intervals.

3 As best fit, logarithmic and linear regression equations were obtained In actual application the difference between these two regression equations was so small that the simple linear regression equation is preferred.

4 In comparison with six other formulas for the relationship between Q-T and R R intervals, most commonly used in clinical application the logarithmic CWS(1) and the linear CWS(2) regression equations gave the least discrepancies to the actual values in 9 subjects near the extremes of the wide scatter of Q-T versus R R intervals.

5 There was excellent agreement in the range of heart rate from 56 to 115 per minute between upper (97 5 per cent) and lower (2.5 per cent) normal limits determined from the percentile distribution and predicted from the linear regression equation

6. The normal limits of the Q-T interval are presented in five ranges of heart rate for convenient clinical application and are believed to be more reliable than those previously suggested. The limitations of prediction of the Q-T interval from the heart rate are discussed

REFERENCES

1 Bazett, H. C. An analysis of the time-relations of electrocardiograms, Heart 7:353 1920.
2. Shipley R. A., and Halloran, W R. Four-lead electrocardiogram in 200 normal men and women, AM. HEART J 11:325 1936.
3 Hegglin, R., and Holzmann, M. Die klinische Bedeutung der verlängerten QT Distanz (Systolendauer) im Elektrokardiogramm, Ztschr klin. Med. 132:1 1937
4. Fridericia, L. S. Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken, Acta med. scandinav 53:489 1920
5. Schlomka, G and Raab, W Zur Bewertung der relativen Systolendauer über die Abhängigkeit der relativen Systolendauer des Gesunden vom Lebensalter Ztschr Kreislaufforsch 28: 673 1936.
6. Ashman, R. Normal duration of Q-T interval, Proc. Soc. Exper Biol. & Med. 40:150, 1939
7 Ashman, R., and Hull, E. Essentials of electrocardiography New York, 1945 The Macmillan Company
8. Schlamowitz, I Analysis of time relationships within cardiac cycle in electrocardiograms of normal men, AM. HEART J 31:329 1946.
9 Mayeda, I On time relation between systolic duration of heart and pulse rate, Acta scholae med univ Imp., Kioto 17:53, 1934.
10. Simonson, E., Brozek, J., and Keys, A. Variability of the electrocardiogram in normal young men, AM. HEART J 38:407 1949
11 Simonson, E., Henschel, A and Keys, A. The electrocardiogram of man in semistarvation and subsequent rehabilitation, AM. HEART J 35:584, 1948.
12 American Heart Association, Committee on Electrocardiography Report Recommendations for standardization of electrocardiographic and vectorcardiographic leads, Circulation 10:564, 1954.
13 Association of Life Insurance Medical Directors and Actuarial Society of America Medico-actuarial mortality investigations, Vol. I New York, 1912.
14. Bardos, J Determination of normal limits from the percentile distribution, Appendix 1 of Simonson,* p. 285
15. Simonson, E. Differentiation between normal and abnormal in electrocardiography St. Louis, 1961, The C. V Mosby Company p. 158.
16. Geppert, M P Die intraindividuelle QT RR Relation im menschlichen Electrokardiogramm, Arch Kreislaufforsch. 18:61 1949
17 Yu, P N G Bruce, R. A., Lovejoy F W J and Pearson, R. Observations on the change of ventricular systole (Q-T interval) during exercise, J Clin. Invest. 29:279 1950.
18. Roehm, D C Kory R. C., and Meneely G. R. Prolongation of electrical systole (Q-T interval) as an added criterion in the Levy anoxia test, Am J Med 14:523 1953

Clinical observations on the antihypertensive response to mebutamate (Capla) in geriatric patients

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Mebutamate (Capla) is a derivative of meprobamate which is reported to possess antihypertensive action.[1] Furthermore, its hypotensive effect is believed to be mediated through a central action on the vasomotor center.[2,3] In order to assess the clinical effectiveness of this compound, a double-blind crossover study [in] a group of patients with well-documented sustained hypertension was undertaken.

Methods and materials

Patients for this study were selected from the cerebrovascular disease clinic of the outpatient department of the University of Oregon Medical School. All patients had been seen at regular monthly intervals for at least 1 year before inclusion in this study. Only patients with mild (diastolic blood pressure of 95 to 110 mm. Hg) or moderate (diastolic blood pressure of 110 to 120 mm. Hg) hypertension were included, i.e., those in whom either rauwolfia compounds and/or thiazide diuretics would be the drugs considered initially for antihypertensive treatment.

Mebutamate in tablets of 300 mg.* and an indistinguishable placebo tablet were used according to a random crossover schedule devised by a third party who had no contact with the study group. Patients were seen at the end of the first week of each month and at the end of each 4-week trial period. At those times the blood pressure was recorded 3 times while the patients were sitting and standing, and they were questioned in regard to untoward side effects. Every 4 weeks the medication was switched to the next unknown tablet, and the process was repeated. In addition, determinations of serum sodium and potassium, blood urea nitrogen, serum glutamic pyruvic transaminase, and alkaline phosphatase were made in each patient before the study was begun and at its conclusion 4 months later. Controlled blood pressures were recorded during the month immediately preceding initiation of the trial of the drug.

Results

Thirteen women and 6 men, who had an average age of 68 (±6) years, were treated for 4 months with mebutamate by means of a double-blind crossover method: 300 mg. of mebutamate 3 times a day or a placebo of identical size and

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*Supplied by Dr. Harry L. Baird, Wallace Laboratories, Cranbury, N. J.

shape. Hypertension had been present in this group for an average of 9 (±5) years and 17 of the 19 patients had received antihypertensive drugs in the past. During the period when the drug was being tried 8 patients were receiving digitalis U.S.P and 2 were taking chlorothiazide because of retention of sodium. The latter 2 patients received chlorothiazide during the period of controlled observation. With these two exceptions, all patients studied had not received antihypertensive therapy for at least 2 months prior to entering the study.

X-ray films of the chest and electrocardiograms had been recorded for each patient within 18 months prior to study. Of the entire group only 2 patients had both a normal electrocardiogram and a normal-sized cardiac silhouette. The electrocardiogram was abnormal in 17 of the 19 patients, and these data are presented in Table I. Ten of the 19 patients had x-ray evidence of cardiomegaly.

The systolic and diastolic blood pressure responses and the mean difference from the control value recorded during each separate month of the trial are summarized in Table II. It is our belief that a drop in diastolic blood pressure of 10 mm. Hg or greater must be produced by any drug which has significant antihypertensive activity. The previously mentioned laboratory studies showed no alteration either before or after therapy.

Drowsiness was the most frequent complaint registered; it reached its maximum incidence during the third month of trial when it occurred in 8 of 18 patients (Table III). In 4 cases this cleared after the first week of therapy, whereas in one other case it was complicated by ataxia which led to exclusion of the patient from further study. The ataxia cleared within 72 hours after administration of the drug was stopped and it did not recur. One patient who reported drowsiness during therapy with mebutamate also complained of it during administration of the placebo (second month). Finally, one patient spontaneously discontinued the drug because of nausea, which cleared after ingestion of the drug was stopped. The one case of ataxia could not be traced to an orthostatic effect from the drug since at the time of complaint the blood pressure which was recorded while the patient was standing was greater than that recorded during the symptom-free control period. Two other patients volunteered the information that mebutamate calmed them down without drowsiness.

Comments

The small and inconsistent mean differences in systolic and diastolic blood pressure observed during periods of treatment with mebutamate were not considered to be clinically significant. It should be pointed out that careful attention was paid to recording blood pressure within 6 hours after administration of the drug since Mulinos and associates[4] have shown that this period is the time of clinically effective drug action. Furthermore, most recordings of blood pressure were made during the second hour after ingestion, a time which is stated to coincide with the time of maximum effect of the drug.[4]

Duarte and co-workers[4] classified 16 of 20 (80 per cent) patients who were given mebutamate alone as unresponsive with regard to antihypertensive effect and pointed out that a much better result could be obtained by combining mebutamate with hydrochlorothiazide (only 9 of 19 unresponsive). This group also noted drowsiness as the most frequent side effect; it occurred in 40 per cent of the patients studied.

Table I. Summary of the electrocardiographic findings recorded in the 19 patients included in this study

ECG interpretation		Number of patients
LVH		6
LVH with old inferior wall myocardial infarction		1
Old inferior wall myocardial infarction		1
Nonspecific S-T and T-wave changes		9
Not receiving digitalis	6	
Receiving digitalis	3	
Normal		2

*LVH: Left ventricular hypertrophy on the basis of at least two of the criteria enumerated by Scott.

Table II Average systolic and diastolic blood pressures recorded during the control period and each month of trial of the drug

	Control period	First month		Second month		Third month		Fourth month	
		Drug	*Placebo*	*Drug*	*Placebo*	*Drug*	*Placebo*	*Drug*	*Placebo*
Number of patients	19	17		5	13	18		12	5
Systolic blood pressure	194 ± 23	180 ± 26		193 ± 58	201 ± 32	179 ± 37		188 ± 33	159 ± 22
Mean difference		−12 5		+6	+2 5	−14 0		−2	−27 5
Diastolic blood pressure	99 ± 8	97 ± 9		99 ± 15	101 ± 11	97 ± 14		100 ± 12	97 ± 9
Mean difference		−3		+3	+1 5	−1 5		+2 5	−6 5

*The results on one patient are not included because the blood pressure was recorded 8 hours after he had received medication.

Table III Incidence and type of side effects experienced

	Control period	First month		Second month		Third month		Fourth month	
		Drug	*Placebo*	*Drug*	*Placebo*	*Drug*	*Placebo*	*Drug*	*Placebo*
Number of patients reporting side effects	0	7 (41%)		0	1 (8%)	10 (56%)		5 (42%)	0
Drowsiness		7 (41%)			1 (8%)	8 (44%)		3 (25%)	
Ataxia						1 (6%)		1 (8%)	
Dry mouth		1 (6%)				2 (12%)			
Nausea						1 (6%)			
Orthostatic weakness								1 (8%)	
Number of patients stopping drug		1				1			

The occurrence of drowsiness in 40 per cent of our patients coupled with the failure to gain a clinically significant drop in blood pressure leads us to the conclusion that mebutamate (Capla) is not a satisfactory antihypertensive agent for the geriatric patient

There was no evidence of renal or hepatic impairment during the period of observation.

Summary

Nineteen geriatric patients with sustained mild to moderate hypertension in addition to cerebrovascular disease were studied for 4 months by means of a double-blind crossover technique in which mebutamate was compared to an inert placebo

No significant antihypertensive effect was observed in the 19 geriatric patients treated with mebutamate (Capla) Over 40 per cent of the patients complained of drowsiness while receiving the drug

REFERENCES

1 Preliminary data, Wallace Laboratories, 1960.
2 Berger F M., and Margolin S. A centrally acting blood pressure lowering agent (W 583) (abstract) Fed. Proc 20:113 1961
3 Kletzkin, M., and Berger F M.. A centrally acting a tipressor agent (abstract) Fed. Proc. 20:113 1961
4 Scott R. C. The electrocardiographic diagnosis of left ventricular hypertrophy Am. Heart J 59 155 1960.
5. Mulinos, M G Schlefor S., Boyd, L J and Cronk, G A. Human pharmacology studies with W 583 (abstract) Fed Proc. 20:113, 1961
6. Duarte C., Brest A. N., Kodama, R., Naso, F., and Moyer J H Observations on the antihypertensive effectiveness of a new propanediol dicarbamate (W 583) Current Therap. Res. 2:148 1960.

Postcardiotomy syndrome after implantation of a pacemaker

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A clinical triad consisting of pericarditis, pleurisy, and pneumonitis was observed to follow mitral commissurotomy in a variable number of cases. At first it was thought to be due to activation of the rheumatic process. Later reports stressed the occurrence of the complication in non-rheumatic cases in which the heart or merely the pericardium was opened for repair of congenital lesions.[2-4] The syndrome was also observed after traumatic injury of the pericardium. In the past year the postcardiotomy syndrome was observed in two of our patients in whom a pacemaker was implanted in the myocardium. These observations are the object of this report.

Report of cases

Case 1. M.S., a 67-year-old man, was admitted to the Maimonides Hospital for the first time on July 18, 1961, after he had suffered syncopal attacks for the preceding 7 months. On the day of admission a bradycardia of 30 per minute was noted. Electrocardiographic records revealed complete atrioventricular dissociation alternating with periods of normal conduction. During syncopal attacks, ventricular standstill was observed and, at times, ventricular tachycardia and fibrillation. On August 2 a miniature transistorized Kantrowitz pacemaker was implanted in a subcutaneous pocket of the abdominal wall. Wire electrodes leading from the pacemaker were inserted into the wall of the left ventricle. The syncopal attacks ceased and the patient was discharged on August 13.

On Aug. [illegible], 1961, the patient complained of severe pain in the precordial area. This pain was aggravated by breathing. He was rehospitalized on August 23. His temperature was 103°F. A loud pericardial friction rub was heard all over the precordium. The white blood count was 15,400 cells per milliliter with 77 per cent neutrophil cells. The sedimentation rate was 30 mm. per hour. The urine showed pus cells which had been also noted during the first admission after use of an indwelling catheter. X-ray study of the chest on August 28 (Fig. 1, *top*) revealed marked pleural effusion at the left side which obscured the left border of the heart, and patchy infiltration of the lung along the right heart border. The cardiac silhouette seemed to be enlarged.

The patient was treated with aspirin and antibiotics. On the second hospital day he was free of pain. The pericardial friction rub was heard for 2 days. Paracentesis of the left pleural cavity yielded 325 ml. of yellow fluid which rapidly coagulated. The urine cleared promptly of pus cells. The temperature returned to normal on the twelfth hospital day. X-ray study of the chest on Sept. 6, 1961, showed clearing of the pneumonitis and pleural effusion and, apparently also, reduction of the size of the heart shadow (Fig. 1, *bottom*). The patient was discharged on September 9.

Case 2. R.C., a 45-year-old woman, was admitted to the Maimonides Hospital on Sept. 10, 1960, after she had suffered frequent attacks of syncope for the preceding 10 months. There was complete atrioventricular dissociation. Syncopal attacks recurred in spite of the use of atropine, ephedrine, Isuprel, and prednisone. The underlying disturbance was ventricular standstill and, at times, ventricular flutter. Therefore, the decision was made to implant an internal pacemaker. Wires of stainless steel were inserted into the wall of the left ventricle. They were connected with a transistorized pacemaker which was strapped around the upper abdominal wall. Thereupon, the syncopal attacks ceased. On March 22, 1961, after a miniature Kantrowitz pacemaker

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Fig. 1. Case 1. Top: Pleural effusion at the left side blurs the left border of the cardiac silhouette. Patchy infiltration of the lung can be noticed along the right heart border. The heart shadow seems to be enlarged. *Bottom:* Nine days after film above. Pleural effusion and pulmonary infiltration have cleared. The size of the cardiac silhouette is reduced.

had become available, the latter was substituted for the externally placed generator and was implanted in a subcutaneous pocket of the abdominal wall.

The patient's condition remained satisfactory until June, 1961, when she noted skipping of beat and complained of a "sinking feeling." X-ray study revealed that one of the bipolar electrodes had slipped out of the wall of the left ventricle. Thoracotomy was performed on June 19 and the loose electrode was reinserted and fixed in the ventricular wall.

Four weeks after this last operation the patient experienced pain in the anterior chest; this pain was aggravated by breathing. The pain subsided after 2 days, but recurred 2 weeks later, on August 6. At this time, it was located substernally, of greater intensity, and associated with a choking sensation. Respiration was shallow because the pain increased on deep inspiration. The patient was rehospitalized on August 7. Physical examination revealed flatness to percussion and diminished breath sounds over the left pulmonary base. X-ray study indicated presence of fluid in the left pleural cavity. The temperature was elevated to 101°F. for 2 days. The white blood count was 10,200 cells per milliliter, with 75 per cent neutrophil cells. On the third hospital day the temperature returned to normal and the chest pain ceased. The patient was discharged on August 9. She was readmitted on Sept. 1, 1961, because of severe recurrent chest pain which, this time, radiated to the neck and ears. The pain increased when the patient turned in bed or took a deep breath. It was relieved by sitting up. The temperature rose to 101.2°F. White blood cell count and differential readings were normal. The sedimentation rate was 40 mm. per hour. X-ray study of the chest revealed haziness at the left pulmonary base. Administration of 400 mg. of Butazolidin per day caused quick relief of pain. The temperature became normal on the fourth hospital day. The patient was discharged on September 15. Later on, progressive reduction of the dosage of Butazolidin was followed by flare-up of chest pain, necessitating an increase in the dosage. Butazolidin had to be continued 9 weeks more, and it was then terminated without ill effect.

Discussion

During the past 17 months pacemakers were implanted in the myocardium of 13 patients at the Maimonides Hospital. Two patients died a few days after operation from causes not connected with the operation. Of the surviving 11 patients, one (Case 1) developed a well-defined postcardiotomy syndrome consisting of pericarditis, pleurisy, and pneumonitis. In Case 2 there was recurrent chest pain, fever, and pleurisy. Signs of congestive heart failure, thrombosis of peripheral veins, or pulmonary infarction were absent. Although there was no unequivocal evidence of pericarditis, the substernal location and character of the pain were highly suggestive of this complication.

The symptoms and signs which presented themselves in the two cases of this report were identical with those observed in the postcardiotomy syndrome which follows operation for rheumatic or congenital heart disease. As in these conditions the complication was benign. The possibility of its occurrence should carry little weight in the decision to implant a pacemaker in a case of Adams-Stokes disease which threatens the patient's life.

Summary

Attention is drawn to the occurrence of a postcardiotomy syndrome after implantation of a cardiac pacemaker. The complication was observed in 2 out of 11 surviving patients in whom recurrent Adams-Stokes attacks necessitated this operation.

REFERENCES

1. Soloff, L. A., Zatuchni, J., Janton, O. H., O'Neill, T. J., and Glover, R. P.: Reactivation of rheumatic fever following mitral commissurotomy, Circulation 8:481, 1953.
2. Ito, T., Engle, M. A., and Goldberg, H. P.: Postpericardiotomy syndrome following surgery for nonrheumatic heart disease, Circulation 17:549, 1958.
3. Liaan, P., Reale, A., and Likoff, W.: Postmitral commissurotomy syndrome: a four year clinical, pathologic and serologic study and its relation to restenosis, Ann. Int. Med. 50:1352, 1959.
4. Johnson, J. L.: Postpericardiotomy syndrome in congenital heart deformities, Am. Heart J. 57:643, 1959.
5. Kroop, G. I., Caruso, I., and Oshrain, C.: Recurrent pleuropericarditis after open-heart repair of congenital cardiac defects, Circulation 24:976, 1961.
6. Wood, P.: Diseases of the heart and circulation, ed. 2, Philadelphia, 1956, J. P. Lippincott Company, p. 538.
7. Kantrowitz, A., Cohen, R., Raillard, H., and Schmidt, J.: Experimental and clinical experience with a new implantable cardiac pacemaker, Circulation 24:967, 1961.

Experimental and laboratory reports

Cholesterol and serum turbidity evaluation measurements in atherosclerosis

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The problem of early diagnosis of atherosclerosis still remains one of the main subjects of work in many laboratories.

Investigations on the epidemiology of myocardial infarction have shown that there is a high incidence of this disease among patients with hypercholesterolemia.[2,11,21,18]

In this work we have endeavored to establish a mean level of total cholesterol in the blood serum of patients with myocardial infarction and hypertension and to compare this with the mean level in healthy subjects. We also desired to find out whether a clinical low-calorie diet poor in fats affects the level of cholesterol in patients with diseases of the coronary arteries. Finally we have attempted to compare the relationship between the pathologic blood serum turbidity curve and the hypercholesterolemia found in coronary atherosclerosis.

The aim of our work has been to establish the relative clinical value of hypercholesterolemia or the pathologic turbidity curve in identifying the disturbances in lipid metabolism which may indicate a predisposition to atherosclerous or its presence.

Material and methods

The material consisted of 350 hospitalized patients with proved acute myocardial infarction, including 65 women and 285 men, and 300 patients with hypertensive cardiovascular disease, including 146 men and 154 women. The average daily consumption of food by each patient came to about 2 000 calories, with 12 to 15 per cent of fats from various sources. The diet was regulated by the Dietetic Department in this hospital. Specimens of venous blood were collected in the morning from fasting patients with myocardial infarction not earlier than after 6 weeks of treatment in the clinic, and from patients with hypertension after they had been in the clinic on an average of 10 days.

In addition, the fasting level of blood serum cholesterol was determined in the outpatient department in 110 patients who had had myocardial infarction and had been discharged from the clinic at least 6 months previously.

The determinations of cholesterol were always made in the same clinical laboratory.

The turbidity of the blood serum in a fasting state and after a fat test meal was determined by our own method.[18] Blood

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for testing was taken after the subject had fasted for at least 12 hours. It was taken again at 3 and at 6 hours after the ingestion of 3 yolks of hens' eggs in 100 grams of milk. To all patients examined we gave a standard fat test without considering the body weight of each individual subject. This fat load was chosen because lipids which are in egg yolks form an emulsion which is sufficiently delicate to be absorbed in the digestive tract. The lipids found in egg yolks include all of the types of lipids which occur in a normal daily diet. This meal proved to be a very practical one to load the patient with lipids because it is easily available, cannot be altered, and does not require weighing since differences in the weights of egg yolks of average size are so minimal that for all practical purposes they can be dismissed. Blood taken when the subject was fasting and that taken after the subject had eaten was allowed to clot and was then centrifuged for 15 minutes, initially at 3,000 r.p.m. and gradually increased to 6,000 r.p.m.

The turbidity of the serum obtained was measured in a Pulfrich photometer against distilled water using an S 61 filter and 1 cm. cuvettes. The results were read on the extinction scale (the red scale of the Pulfrich photometer).

In this way the unit of turbidity is a logarithmic function of the apparent serum absorption.

Our use of this extinction scale gave absorption values for serum between 0.05 and 1.8, in contrast to the high values obtained by other authors who used millimetric or other scales. Knowing the exact conditions of the determinations by other authors and the type of equipment used by them, one can recalculate their results and obtain comparative data. We chose the Pulfrich photometer because it is most common in Poland, is simple to use, and gives clear and exact results.

This method differs fundamentally from the loadings previously applied both in the quantity and quality of the fat given. Those examined by this method receive only about 20 grams of lipids, contained in the three egg yolks and 100 grams of milk, whereas other workers give 60 to 75 to 100 or more grams of fat in the form of cream, butter, or oil, sometimes with the addition of eggs.[1-4,11,21,25,27,28]

The levels of cholesterol found in the patients were compared with the normal levels established by Gabryelski and Ciba[18] for healthy subjects living in Cracow. The frequency of appearance of hypercholesterolemia and the pathologic turbidity of the serum in the appropriate groups of patients were obtained by comparing the highest average deviations in healthy subjects with the results obtained from the patients examined.

The statistical calculations were made according to the formulae

$$\bar{x} = \frac{\sum_{i=1}^{n} x_i}{n}$$

and

$$\delta = \frac{\sum_{i=1}^{n} \bar{x} - x_i}{n}$$

in which $\bar{x}$ denotes the arithmetic mean (for turbidity in units of extinction and for total cholesterol in milligrams per cent), δ = the average deviations from the arithmetic mean (in units as above), x_i = the particular values of turbidity of total cholesterol, $i = 1,2,3 \ldots n$, n = the number of tests, $\bar{x} - x_i$ = the successive absolute values of the differences between the arithmetic means and the particular values of turbidity or total cholesterol, Σ = the sign of the sum.

Results

It appears that the mean levels of cholesterol in the appropriate age groups in the patients with myocardial infarction treated in the clinic were considerably higher than those of the normal group. The height of the cholesterol level as compared with the normal means in the fourth decade in men and in the sixth in women is striking.

Hypercholesterolemia among the group of patients with myocardial infarction treated in the clinic as compared with the highest average deviations from the normal mean was found in only 29 per cent of those examined.

The fasting level of cholesterol was determined in 110 postinfarct outpatients who had been discharged from the clinic

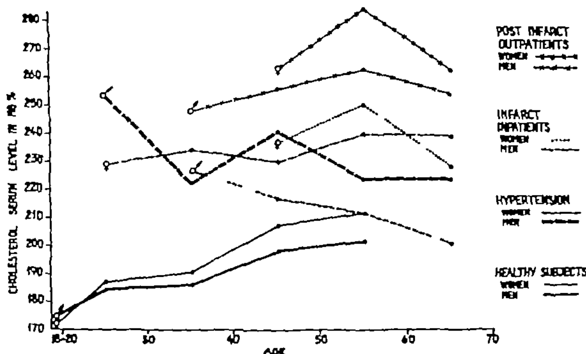


Fig. 1. Mean levels of cholesterol in different decades and sexes in healthy subjects and patients with myocardial infarction or hypertension.

at least 6 months previously. As is evident from Fig. 1, the mean level of cholesterol in this control group increased considerably in all decades, and was higher in men than in women under conditions of home nutrition. The increase in cholesterol in men over 60 was particularly striking. In this group the incidence of patients with hypercholesterolemia also rose considerably, reaching in general 57.2 per cent of those examined—61.9 per cent of the women and 56.9 per cent of the men.

We attribute the rise in the mean level of cholesterol and the increase in the number of patients with hypercholesterolemia in the group under discussion to the more abundant food and the greater consumption of fat under home conditions. Contributing to this also would be the circumstance that the rise has a more marked effect on men who traditionally are accustomed to eat more at home than their wives do. This assumption was confirmed by Chudzkiewicz[4] in the same group of patients under home conditions.

For investigations closely connected with atherosclerosis, we selected not only patients with cardiac infarction but also patients with hypertension because postmortem examinations of those who have died of hypertension show atherosclerotic lesions in the coronary vessels of 85 to 90 per cent of these patients.[9,20,28]

The results of examination in patients with hypertension indicated that the average levels of cholesterol are considerably higher in relation to the normal means and that the level in the youngest of men is particularly remarkable. In general, hypercholesterolemia was found in 37 per cent of the patients with hypertension.

The results of the examinations are presented in Table I, which shows the average levels of all three groups of patients, and in Table II, which gives the calculation of the significance test (t) for the mean levels of cholesterol.

On the basis of Table II, it appears that the differences in the average levels of cholesterol are significant ($t > 3$) and are more frequently repeated in the total figures than in the age groups. Among the age groups the significance test results are highest in men between 50 and 60 years of age. In general, the significance-test results are higher among men than among women. Deserving of emphasis is the fact that in men the significant differences be-

Table I Mean levels of cholesterol (x̄) and average deviations (δ) in different decades and sexes in healthy subjects and patients with myocardial infarct or hypertension

		Age						Total
		18-20	21-30	31-40	41 50	51-60	Over 60	
Healthy subjects								
Men	n	25	25	27	27	25		129
	x̄	174 8	183 5	186 8	198 0	201 5		188 8
	δ	24 1	24 5	41 2	37 9	36 8		35 3
Women	n	25	29	31	25	28		138
	x̄	173 9	187 0	190 3	206 9	211 4		203 7
	δ	26 9	34 5	28 4	35 8	38 9		35 3
Infarct inpatients								
Men	n			16	78	117	72	283
	x̄			226 3	216 6	211 3	200 9	211 0
	δ			43 3	45 9	44 6	47 2	43 7
Women	n				16	4	21	61
	x̄				236 0	249 9	227 6	233 6
	δ				48 9	64 2	51 6	57 1
Postinfarct outpatients								
Men	n			5	28	38	17	88
	x̄			247 3	255 0	262 6	233 7	253 3
	δ			50 4	50 7	52 0	57 5	52 9
Women	n				4	12	4	20
	x̄				262 5	283 5	261 0	275 0
	δ				74 0	74 1	39 6	69 3
Inpatients with hypertension								
Men	n		8	15	29	53	36	142
	x̄		233 2	221 6	239	223 7	223 7	226 7
	δ		74 1	32 5	45 7	43 3	35 4	44 1
Women	n		9	9	33	56	44	151
	x̄		228 5	234 2	229 3	239 6	238 5	236 0
	δ		34 7	41 9	38 7	51 8	46 0	46 2

Table II Significance test (t) for cholesterol level averages

	Men						Women					
	Age (yr)					Total	Age (yr)					Total
	21 30	31 40	41 50	51 60	Over 60		21 30	31 40	41 50	51 60	Over 60	
Healthy subjects—Infarct inpatients		3 0	2 0	1 1		5 7			2 0	2 6		4 4
Healthy subjects—Postinfarct outpatients		2 5	4 8	5 5		10 0			1 5	3 2		4 5
Healthy subjects—Hypertensive patients	2 6	3 0	3 7	2 3		7 9	3 0	3 0	2 2	2 7		4 7
Infarct inpatients—Postinfarct outpatients		0 8	3 5	5 4	3 5	6 8			0 7	1 3	1 8	2 1

Table III *Mean level (x̄) of blood serum turbidity and average deviation (d) during fasting and after loading with lipids in 120 patients with myocardial infarction and 300 patients with hypertension*

		Age														
		31-40			41-50			51-60			61-70			71-80		
		Fasting	After 3 hr	After 6 hr	Fasting	After 3 hr	After 6 hr	Fasting	After 3 hr	After 6 hr	Fasting	After 3 hr	After 6 hr	Fasting	After 3 hr	After 6 hr
Infarction																
Men	x̄	0.17	0.56	0.27	0.16	0.46	0.27	0.12	0.38	0.19	0.11	0.37	0.18	0.07	0.35	0.22
	d	0.05	0.06	0.13	0.06	0.13	0.12	0.03	0.10	0.06	0.03	0.13	0.06	0.02	0.11	0.10
Women	x̄				0.13	0.45	0.21	0.15	0.33	0.25	0.14	0.44	0.29			
	d				0.04	0.09	0.05	0.03	0.11	0.08	0.03	0.13	0.08			
Hypertension																
Men	x̄	0.13	0.44	0.21	0.13	0.41	0.22	0.13	0.34	0.20	0.11	0.30	0.18			
	d	0.04	0.15	0.09	0.04	0.17	0.11	0.04	0.10	0.07	0.02	0.10	0.07			
Women	x̄	0.11	0.34	0.22	0.12	0.31	0.17	0.12	0.36	0.23	0.13	0.32	0.19			
	d	0.02	0.11	0.11	0.03	0.09	0.06	0.03	0.13	0.12	0.04	0.10	0.06			

tween the levels of cholesterol in patients treated in the clinic and the levels in out patients are very frequently repeated whereas in women this difference is not significant.

From the results presented it may be seen that an increase in cholesterol is closely associated with the development of atherosclerosis. Thus, as we have shown in the test, the statistical data indicate that hypercholesterolemia in patients with

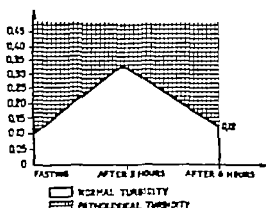


Fig. 2 Fields of normal and pathologic turbidity in venous blood serum, during fasting and after loading.

atherosclerosis varies within the range of 29.7 to 37 per cent in the clinic but goes up to 57.2 per cent, on the average, in the outpatient department. It follows from this that individually in a fairly large number of atherosclerotic patients the cholesterol content varies within the average normal limits or is even lowered.

Discussion of the assumptions of serum turbidity curve tests

The clearness of the serum measured turbidimetrically in extinction units preserves a constant value physiologically.

The rise in serum turbidity after the consumption of fat is a sign of a transition in bulk of chylomicrons from the alimentary canal to the stores of fat in the body. This phenomenon has very little influence on the level of cholesterol in the blood since the chylomicrons contain only an insignificant quantity.[4] This detail calls attention to the fact that hyperlipemia should not be identified with hypercholesterolemia. In the clinic pathologic blood serum turbidity is found without any rise in the level of cholesterol and vice versa hypercholesterolemia is found without any pathologic turbidity of the blood serum.

According to L. E. French and associates[7] alimentary serum turbidity under normal conditions of fat metabolism disappears gradually as a result of the penetration of unchanged chylomicrons from the circulating blood through the walls of the capillary vessels to the stores in the organism principally to the liver. In addition the activity of the enzymatic hydrolyzing which like heparin leads to the breakdown of the chylomicrons into glycerol and fatty acids contributes to the clearing of the serum. No small role in the clearing of the serum is also played by the phagocyte processes.

It was Moreton who first connected the etiopathogenesis of atherosclerosis with the presence of chylomicrons in the blood supposing that an excess of these maintained for years would lead to infiltration of the lining of the arteries by the fat and cholesterol contained in the chylomicrons.

Starting from the hypotheses set forth by many authors cited above in the description of our methods, we have based our investigations of fat metabolism on testing the time taken by turbid serum to clear in a fasting state and after ingestion of fats. In our investigations we[34] established statistically that in atherosclerotic patients the blood serum turbidity curve is sufficiently characteristic for the diagnosis of atherosclerosis.

The normal values of the turbidity curve for the fasting state and after the consumption of 3 egg yolks, according to our investigations, which we present in Fig. 2 are contained within the limits of the light field which may be expressed numerically in healthy subjects thus: when fasting 0.07 ± 0.03 at the end of 3 hours after loading 0.24 ± 0.09 and at the end of 6 hours after loading 0.09 ± 0.03 turbimetric units. A pathologic condition is assumed to exist when fasting serum turbidity exceeds the highest deviation from the normal mean which we have established as 0.10 units, or when the peak of the curve is over 0.33 units, or when turbidity over 0.12 units lasts for more than 6 hours after loading with lipids: this is shown in the cross-hatched part of Fig. 2.

Certain conditions should be observed when carrying out the test if the curve is to be evaluated correctly. Before the test the subject should remain fasting for at least 12 hours and loading should be carried out under conditions of complete physical and mental rest.

In evaluating atypical turbidity curves, or when the results deviate from the clinical picture, one should take into consideration concurrent states of generally intensified metabolism and conditions which render it difficult to absorb fat from the alimentary canal.

The results of the test under discussion are given in Table III. As may be seen from this table, the average serum turbidity values in both groups of patients exceed the upper limit of average deviations in healthy subjects either when fast

Table IV. Percentages of pathologic cholesterol level and turbidity in patients with myocardial infarction and hypertension

	Sex	Number examined	Percentage of increased cholesterol	Percentage of pathologic serum turbidity
Patients with myocardial infarction in the clinic	M	285	29.4	90.8
	W	65	30.7	90.9
Total		350	29.7	91.6
Ambulatory patients with myocardial infarction	M	89	36.1	
	W	21	61.9	
Total		110	57.2	
Patients with hypertension in the clinic	M	146	36.3	80.8
	W	154	37.6	82.4
Total		300	37	81.6

ing or after loading with the exception of fasting turbidity values in patients over 70 years of age. In men up to 50 years old the turbidity values are higher than those in women whereas in women it is only after the age of 50 that increases in turbidity deviate more from the normal.

In order to facilitate the comparison of these results as regards the frequency of appearance of hypercholesterolemia and hyperlipemia in atherosclerotic patients, we give the corresponding data in Table IV. The percentages given in this table were obtained from a detailed analysis of the results of investigations on a particular patient taking into account the highest deviations from the normal mean. In this way we ascertained that, in those examined general disturbances in the fat metabolism occurred in 91.6 per cent of the patients with myocardial infarction and in 81.6 per cent of the patients with hypertension.

It should be emphasized that fasting serum turbidity in patients in the initial stage of recent infarction lies within normal limits.

In our experience hyperlipemia was also found both in the fasting state and after a fat test meal in patients in the course of Sheehan's disease, in thyroid insufficiency, often in diabetes, in nephrosis and in essential hypercholesterolemia.

Conclusion

The results of our investigations confirm the views of many authors that the average level of *serum cholesterol is higher in* those with atherosclerosis than in healthy subjects but that individually hypercholesterolemia does not appear in more than 57.2 per cent of the patients in this group. We have shown that the height of the level of serum cholesterol may depend also on the actual mode of nutrition and thus, the percentage of hypercholesterolemia in atherosclerotic patients is variable and may fall on the average to 29.7 per cent.

The characteristic turbidity curve which we found to lie within the limits of 81.6 per cent to 91.6 per cent is a much more constant and frequent sign in atherosclerotic patients than is hypercholesterolemia.

Hyperlipemia has already been associated with the etiopathogenesis of atherosclerosis by many authors. The results of tracing the evolution of conditions of those with family hyperlipemia,[13] a rise in blood coagulation after ingestion of fat,[9,12] and J. B. Duguid's theory of the etiopathogenesis of atherosclerosis[4] also favor this view. It is also not without significance that, in subjects with coronary disease, attacks of pain and changes in the electrocardiographic curve often appear after the consumption of fat,[14] and that treatment with heparin or the administration of pulverized dried gastric mucin have beneficial effects on this condition.[22]

Our investigations carried out for many years and based on thousands of examinations, indicate that hyperlipemia in the fasting state occurs much more frequently than is at present supposed. In connection with this, by taking the clinical signs of hyperlipemia into consideration, we now find a clearer explanation of the syndrome of abdominal symptoms in many patients with coronary disease.

In the final evaluation of the biochemical indices of atherosclerosis under discussion we have concluded that by following the turbidity curve we get a better picture of the behavior of the fat metabolism than we do from a single test of the level of serum cholesterol. In clinical practice, however, the two examinations complement each other since hypercholesterolemia may have no effect on the clearness of the serum and vice versa, as more often *happens the turbidity curve has no relation* to the total concentration of cholesterol in the blood serum.

Summary

Investigations were carried out in the clinic on 350 patients who had had myocardial infarcts and on 300 patients with hypertension.

The total cholesterol in the blood serum during fasting and the lipid curve after the ingestion of 3 egg yolks were determined in these patients.

The results of these investigations confirm the views of many authors that the average level of serum cholesterol is higher in patients with atherosclerosis than in healthy subjects, but that among this

group of patients hypercholesterolemia does not occur individually in more than 57.2 per cent of those examined

It has also been shown that the level of serum cholesterol depends on the actual mode of nutrition so that the percentage of atherosclerotic patients with hypercholesterolemia is variable and may fall from 57.2 to 29 7 per cent during the application of a low-calorie diet that is poor in fats.

The characteristic turbidity curve which was found to be within the range of 81.6 per cent to 91 6 per cent is a much more persistent and frequent sign than hypercholesterolemia in patients with atherosclerosis.

In our definitive evaluation of cholesterol and turbidity in atherosclerosis we conclude that following the turbidity curve gives a better idea of the behavior of the fat metabolism than do single tests of the level of serum cholesterol

REFERENCES

1 Barritt, D W Alimentary lipaemia in men with coronary artery disease and its controls, Brit. M J 4993:640, 1956.
2. Bronte-Stewart, B.: The effect of dietary fats on the blood lipids and their relation to ischaemic heart disease, Brit. M. Bull. 14:243 1958.
3. Chra, R., Dvorak, L., and Donocik, A. The course of postprandial turbidity in relation to atherosclerosis, Cas Lek. Cesk. 96 1003 1957
4 Chodzkiewicz, T : The aetiopathogenesis of myocardial infarction, Pol Tyg. Lek. 16(28) 1066 1961.
5 Duguid, J B Diet and coronary disease, Lancet 1:891 1954.
6. Fredrickson, D S. Some biochemical aspects of lipid and lipoprotein metabolism, J A M.A. 164 1895, 1957
7 French, L. E., Morris, B., and Robinson, D S. Removal of lipids from the blood stream, Brit. M. Bull. 14:234, 1958
8. Friedberg, C. K. Diseases of the heart, Philadelphia, 1956, W B Saunders Company
9 Fullerton, H W Davie, W I. A., and Anastasopoulos, G. Relationship of alimentary lipaemia to blood coagulability Brit. M. J 2:250 1953
10. Gabryelski, W., and Ciba, T Total and free blood cholesterol in healthy persons, Pol. Tyg Lek. 15(12) 437 1960.
11 Gofman, J W., et al. Evaluation of serum lipoprotein and cholesterol measurements as predictors of clinical complications of atherosclerosis report of a cooperative study of lipoprotein and atherosclerosis, Circulation 14:691 1956
12. Ignatowska, H. The lipaemic curves in atherosclerosis, Pol. Arch. Med. Wewnet. 29:639 1959
13 Keys, A. Diet and the epidemiology of coronary heart disease, J.A.M A. 164 1912 1957
14 Kuo, P T and James S. R. Angina pectoris induced by fat ingestion in patients with coronary artery disease, J.A.M.A. 158:1008, 1955.
15. Malmros, H Swahn, B., and Friedman, E. Essential hyperlipaemia, Acta med. scandinav 149:91 1954.
16 Mattingly T W et al Lipid studies in health and disease J.A.M.A. 170:536 1959
17 Mitchell, J and Bronte-Stewart, B. Alimentary lipaemia and heparin clearing in ischaemic heart-disease, Lancet 1 167 1959
18. Moreton, J R. Atherosclerosis and alimentary hyperlipaemia, Science 106 190, 1947
19 Pool, J C F Fats and blood coagulation, Brit. M Bull. 14:253 1958
20 Rinzler S. H The clinical aspect of arteriosclerosis, Springfield, Ill., 1957 Charles C Thomas, Publisher
21 Raffi, V and Rossi, B. Plasma turbidity changes and electrocardiographic alterations induced by alimentary hyperlipaemia in anginal patients before and after the administration of gastric mucin, Circulation 18:400 1958.
22 Schwartz, L., Woldow A and Dunsmore R A. Determination of fat tolerance in patients with myocardial infarction, J.A.M.A. 149:364 1952.
23 Smolenskij W C The development of arterial atherosclerosis in patients with normal or high arterial blood pressure, Terapevt Arkh. 30(8): 47 1958
24. Tochowicz, L., and Dembkiewicz, W Turbidity of the blood serum in patients with atherosclerosis of the coronary vessels, Minerva med. 49(55) 2620 1958
25 Woldow A., Chapman, J E and Evans, J M.: Fat tolerance in subjects with atherosclerosis, Am. Heart J 47:565, 1954

Atherosclerosis and levels of serum cholesterol in postmortem investigations

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Elevation of the levels of serum cholesterol in patients suffering from atherosclerosis is often cited in support of the metabolic theory of the development of atherosclerosis.

The importance of the level of cholesterol in the clinical diagnosis of atherosclerosis is somewhat weakened by the fact that up until now the marked individual variations in the level of cholesterol in patients as well as in healthy individuals has not been adequately explained and defined. In pathogenetic and clinical considerations, the studies of Gofman and colleagues[4] and Gertler and colleagues[3] are of primary importance. They found a higher incidence of coronary disease in persons with elevated levels of cholesterol. This problem has also been investigated by way of autopsy. In 1936 Lande and Sperry[7] in postmortem investigations did not find a correlation between the level of cholesterol in blood serum and the degree of atherosclerotic changes. Similar investigations have been carried out by Spain, Bradess and Greenblatt[10] on the basis of determinations of beta lipoproteins in blood serum. Some partly positive results were obtained.

Our investigations were designed to show whether a relationship exists between the level of serum cholesterol and the intensity, localization, and type of atherosclerotic changes. The investigations were based on the autopsy material of the Institute of Forensic Medicine in Cracow. The results were compared with the studies of Tochowicz and colleagues[11] as well as those of Gabryelski and Ciba.[3] These authors investigated the level of serum cholesterol in patients treated for myocardial infarction and hypertensive disease and in clinically healthy individuals from the same population as our subjects.

Methods and results

A group of 106 persons who were over 20 years of age, and who had died suddenly from natural or violent causes were the object of our investigations. The autopsies were carried out in the Institute of Forensic Medicine of the Academy of Medicine in Cracow. The blood was drawn from the external jugular vein up to 20 hours after death. Only those cases were considered in which traces of hemolysis were not confirmed by spectroscopic examination. The experimental observations showed that the level of cholesterol does not depend on the vessel from which the sample of blood is drawn nor the degree of blood lost.[1] Comparative tests were made in only 2 cases. The level of cholesterol in blood

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taken immediately before, and that in blood taken a few hours after death were 12 and 7 mg per cent respectively. The level of total cholesterol was investigated by routine clinical methods.

Particular attention was paid during autopsy to the precise localization and degree of atherosclerotic changes in the coronary arteries, the aorta, and the arteries at the base of the brain. Atherosclerosis found in postmortem investigations was classified into four groups according to a scheme the value of which was confirmed in previous studies.[4] The atherosclerotic alterations were classified as "advanced," "medium," "mild," and absent (cases "without atherosclerosis").

Independently of the afore-mentioned classification, the whole material was divided into the following groups: Group 1—Cases designated further as the group of coronary deaths, e.g., cases of coronary atherosclerosis with or without myocardial infarction, with coronary thrombosis, with advanced coronary stenosis, or with rupture of the heart as a result of infarction or scars from previous infarction. Group 2—All other cases of confirmed atherosclerosis, without regard to the cause of death. Group 3—Cases without atherosclerosis.

Because of the influence of different diseases on the level of serum cholesterol, additional macroscopic examinations of lesions in the liver, kidneys, and thyroid gland were made. The state of nutrition, quantity of alcohol consumed and tobacco smoked, as well as occupation and social conditions were also considered.

In 43 cases histologic preparations from the aortic arch and the proximal part of the left coronary artery were examined. Paraffin sections were stained with hematoxylin and eosin and also with Gomori's silver impregnation method for fibrous elements. Frozen sections were also examined for lipids (Sudan III, Nile blue) and for free cholesterol by Windaus digitonin method.

In order to make preliminary calculations all the cases were divided into two groups without regard to age or sex. These two groups were comprised of those cases without atherosclerosis and those with atherosclerosis regardless of the severity of the lesions. It was found that the difference between the average levels of cholesterol in these two groups was 35 mg per cent, which is statistically insignificant ($t = 2.9$).

The atherosclerotic group was divided into subgroups "advanced," "medium," and "mild." On the basis of this division it was shown that differences in average levels of cholesterol were statistically significant (t greater than 3) only between the subgroup of advanced atherosclerosis and the group without atherosclerosis (Table I). Another method of representing the results was by graphs in which the different cases (taking into consideration the difference in sex) were plotted in relation to two axes (x = age, y = level of cholesterol). From Fig. 1 it appears that the cases with atherosclerosis are found mainly in the interval between 200 and 300 mg per cent cholesterol. In the cases without atherosclerosis the levels of cholesterol were about 50 mg per cent lower. There was no distinct influence of age on the level of cholesterol. In order to compare postmortem findings and clinical investigations on a mutual basis, we have selected two groups which appear to us to be homogeneous, namely, cases of coronary death and cases without atherosclerosis. The most interesting group from our point of view was the first because of the correspondence to clinical coronary disease.

The difference between the average level of cholesterol in the group without atherosclerosis and that in the group of coronary deaths ($t = 3.3$) is similar to the difference between cases without atherosclerosis and cases of advanced atherosclerosis. The mean level of cholesterol in 12 cases of fresh infarction was lower than in all cases of coronary death (Table II and Fig. 2). Differences in the results of biochemical tests in cases of recent infarction have already been found previously in postmortem studies. Similarly, clinical observations also indicated that levels of cholesterol in the blood of patients treated for cardiac infarctions were decidedly lower than in patients with healed infarctions controlled after several months in the outpatient department.[11]

The material which related only to

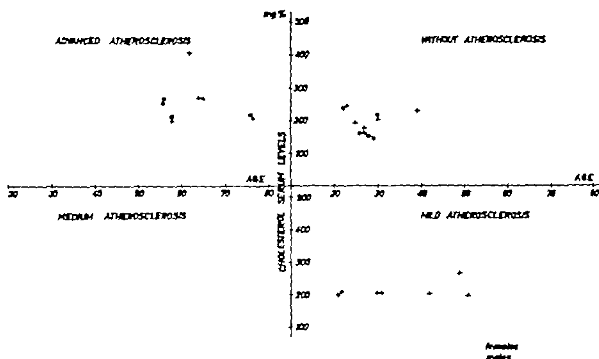


Fig. 1. Relation of levels of cholesterol to age in material classified into groups according to the intensity of the atherosclerotic process.

Table I

Group	*Number of cases*	*Cholesterol levels (mg %)*	*Test of significance (t)*	*Mean age (Age groups)*	*Sigma*
Without atherosclerosis	25	205	3.2	27.7 (20–35)	48.8
Advanced atherosclerosis	31	260		63.4 (55–80)	76.9
Medium atherosclerosis	22	226		59.1 (45–65)	49.4
Mild atherosclerosis	28	229		44.6 (30–50)	46.7
Atherosclerosis total	81	240		55.5 (40–70)	62.6

males was analyzed separately. A similar relationship was confirmed. Fig. 3 gives a summary of all values of the average levels of cholesterol in the different groups. For purposes of comparison the group shown in Fig. 3 gives the average levels of cholesterol found in clinically healthy persons and in patients with infarcts.

The level of serum cholesterol in our group of coronary deaths is very similar to the curve established by Tochowicz and co-workers.[11] On the other hand the corresponding values for clinically healthy persons, established by Gabryelski and Ciba[9] lie distinctly below the average for our group of cases without atherosclerosis and are closer to the results obtained by American investigators.

We considered also whether we could explain the well-known individual fluctuations in the levels of cholesterol by alterations in other organs. But this analysis did not give positive results. We thought that alterations in the thyroid gland would be

the easiest to evaluate because the functional influence of this gland on the level of cholesterol is well known. However on the basis of morphologic changes, deductions as to the functional state of the thyroid gland could not be made. Nevertheless, it is worth noting that in 66 per cent of the cases in the group of coronary deaths in our material the changes defined macroscopically included diffuse nodular and cystic goiters calcifications fibrotic changes, and simple atrophy of the gland. In the other groups, such alterations were present in only about 20 per cent of all cases. Uotila and colleagues[21] also found anatomic changes in the thyroid gland in a considerable percentage of individuals stricken with sudden cardiac death. Nikkilä and Karlsson[9] have not found functional alterations of the thyroid gland in clinical investigations of individuals with heart infarct.

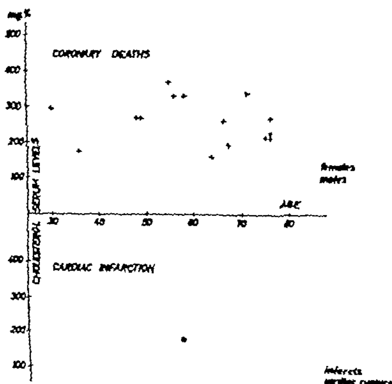


Fig. 2. Relation of levels of cholesterol to age in the group of cases of coronary death and in the subgroup of cases of cardiac infarction. In the bottom section of the figure, the small dots indicate infarcts and the larger ones indicate cardiac rupture.

Table II

Group	*Number of cases*	*Cholesterol levels (mg. %)*	*Test of significance (t)*	*Mean age (Age group)*	*S [illegible]*
*Coronary death	31	261	3 3	60 3 (50-80)	74 4
Without atherosclerosis	25	205		27 7 (20-35)	48 8
Recent cardiac infarction	12	235		60 9 (50-80)	54 3

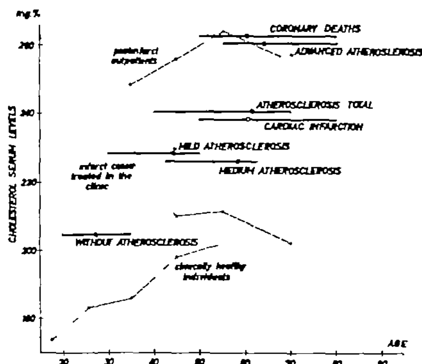


Fig. 3. Mean levels of serum cholesterol in different groups of cases, also shown in relation to age. Horizontal lines show the age range of the majority (70 to 80 per cent) of the cases; the mean age in each group is indicated by points. The dashed lines show the mean levels of cholesterol according to age groups in clinically healthy individuals, and in a group of patients with cardiac infarction who were followed as outpatients after clinical treatment.

Since the results of comparison of the levels of serum cholesterol with macroscopic atherosclerotic changes were not unequivocal, we compared the microscopic alterations in arteries with the levels of cholesterol. Histologic investigations were carried out in 11 cases of coronary death, in 8 cases without atherosclerosis, and in 24 other cases with atherosclerosis. Microscopically the arteries examined showed a considerable variety of alterations. The group of cases of coronary death did not show any specific microscopic changes. Therefore, of the various microscopic features which were analyzed, only those showing the most consistent behavior were considered; these included the foci of atherosclerotic necrosis, the presence of cholesterol, character of fatty degeneration, aggregation of inflammatory cells, and foci of calcification. However, we did not find any relationship between the various features, their intensity, and the levels of cholesterol in the blood.

A division of the cases into four groups was made on the basis of the above-mentioned microscopic features. We found only old persons (up to 75 years) in a group of 6 cases with marked preponderance of fibrotic changes and calcification. In a group with greater preponderance of atherosclerotic necrosis and abundant deposits of cholesterol the majority of cases were coronary deaths. We have not found, however, any particular difference between average levels of cholesterol in separate groups divided according to microscopic changes. Finally, we were not able to establish a relationship between the total level of serum cholesterol and the free cholesterol in the atherosclerotic infiltrations. However, it should be remembered that total cholesterol was determined in the blood serum, and free cholesterol in the walls of the arteries.

Discussion

We have attempted to compare the level of serum cholesterol of persons who died suddenly from various causes with the

intensity and localization of atherosclerotic changes found by postmortem investigations in the more important arteries. The results of our investigations were similar to the results of clinical investigations. The autopsy material examined was from the same population in which the clinical investigations were made.

We have confirmed a higher average content of cholesterol in the group of cases with intensive atherosclerosis and also, using another classification, in the group of coronary deaths. The average level of cholesterol found in patients suffering from cardiac infarcts was slightly lower than that in the whole group of patients who died coronary deaths. In all other groups the differences encountered were not statistically significant. We have not found a definite relationship between the level of cholesterol, age of the patient, and localization of the atherosclerotic changes. The level of serum cholesterol in all cases with atherosclerotic changes was higher in only 37 per cent (over $\bar{x}$ + 1 sigma = 254 mg. per cent), i.e., two thirds of those who died with confirmed atherosclerosis had levels of serum cholesterol lower than the upper limit of normal values.

The very significant individual fluctuations in serum cholesterol were impossible to explain on the basis of coexisting alterations of other organs. One fact merits attention, namely, the frequency of macroscopic alterations of the thyroid gland in the group of cases of coronary death. Also the histologic investigations have not given basis for binding conclusions. From our investigations it would appear that even the possibility of objective evaluation of atherosclerosis during autopsy does not diminish the effect of the scatter of individual levels of cholesterol in the different groups of cases.

Although the material which we studied was small, it was at least homogeneous. The entire group of coronary deaths comprised cases of sudden death which occurred in people who were in full health, or which was preceded by a short period of illness. From this it can be concluded that the level of serum cholesterol found by us closely approximates the true level of cholesterol before illness and death. In our opinion, this condition could not be fulfilled by investigations of levels of cholesterol in blood obtained from persons who died after a prolonged hospitalization during which they were subjected to various diets, pharmacologic treatment, and influence of prolonged agony on the biochemistry of the blood.

In reference to the problem of etiopathogenesis of atherosclerosis as a whole, we can only conclude, on the basis of our study, that the level of cholesterol does not stand in direct relation to the intensity and localization of atherosclerotic changes.

Summary

In our work we have compared the postmortem findings in material from the Forensic Institute in Cracow (persons who died suddenly from various causes) with the levels of cholesterol and the intensity and localization of atherosclerotic lesions. The total content of cholesterol in the serum was determined in 106 cases. Microscopically, examinations were made in 43 cases. The free cholesterol in atherosclerotic alterations was also investigated by the digitonin method.

It was confirmed that the average level of cholesterol in individuals suffering from atherosclerosis (240 mg. per cent) is higher than that in those without atherosclerotic symptoms (205 mg. per cent). These differences are statistically significant only in the group of cases of advanced atherosclerosis (260 mg. per cent) and in the group of cases of sudden death from coronary sclerosis (261 mg. per cent). No significant statistical difference was found in the other groups, which differed from each other only in the degree of atherosclerotic changes. The average level of serum cholesterol in people who died from cardiac infarction (238 mg. per cent) was lower than the level of cholesterol in the whole group of persons who suffered sudden coronary death. Microscopic examinations gave no basis for binding conclusions. Also, no relationship was found between the free cholesterol in arterial walls and the total cholesterol in blood serum.

The results of these examinations do not differ practically from the results obtained in analogous examinations in health and disease with atherosclerosis conducted by

the same methods, in the same laboratory and in the same populations.

REFERENCES

1. Adamczyk, B., Marczyńska, A., Ostrach, J., and Gedlicka, O.: Wpływ krwotoku na zachowanie się cholesterolu oraz potasu i sodu i chloru we krwi. Pol. Tyg. Lek. 14(1):15, 1959.
2. Gabryelski, W., and Ciba, T.: Poziom cholesterolu całkowitego i wolnego w surowicy krwi zdrowych z uwzględnieniem płci i wieku. Pol. Tyg. Lek. 15(12):417, 1960.
3. Gertler, M. M., Woodbury, M. A., Gottsch, L. G., White, P. D., and Rusk, H. A.: The candidate for coronary heart disease. Discriminating power biochemical, hereditary and anthropometric measurements. J.A.M.A. 170:149, 1959.
4. Gofman, J. W., Hardin, B., Lyon, T., Lindgren, F., Strisower, B., Colman, D., and Herring, V.: On evaluation of the lipoproteins and cholesterol measurements as predictors of clinical complications of atherosclerosis. Circulation 14:691, 1956.
5. Jaegermann, K., and Marek, Z.: Badania nad nasileniem miażdżycy w materiale sekcyjnym w latach 1900-1958. (In press.)
6. Kritchevsky, D.: Cholesterol, New York, 1958, John Wiley & Sons, Inc.
7. Lande and Sperry: Cited from Kritchevsky[6] and Liebig.[8]
8. Liebig, H.: Cholesterinämie und Atherosklerose, Klin. Wchnschr. 20:538, 1941.
9. Nikkilä, A., and Karlsson, K.: Thyroid function and clinical coronary heart disease. Acta med. scandinav. 166:195, 1960.
10. Spain, D. M., Bradess, A. V., and Greenblatt, I. J.: Postmortem studies on coronary atherosclerosis, serum beta-lipoproteins and somatotypes, Am. J. M. Sc. 229:294, 1955.
11. Tochowicz, L., Paryk, S., and Denikiewicz, W.: Ocena wartości badania cholesterolu i lipemii pokarmowej w miażdżycy. Pol. Tyg. Lek. 15(20):737, 1960.
12. Uotila, U., Raekallio, J., and Ehrnrooth, W.: Goitre and arteriosclerosis, Lancet 2:171, 1958.

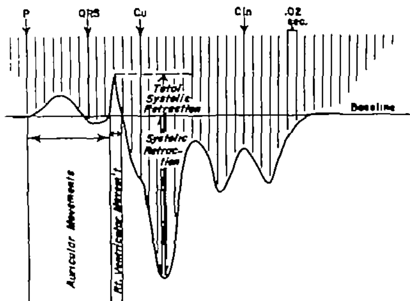


Fig. 1. Schematic drawing of the normal K trace. The onset of the P wave is indicated by arrow *P*, the onset of the QRS complex in the ECG is indicated by arrow *QRS*, the upstroke in the carotid pulse is indicated by arrow *Cu*, and the incisural notch in the carotid pulse is labeled *Cin*. The auricular movements begin after the onset of the P wave and may extend up to approximately 0.04 sec. after the onset of the QRS complex of the ECG. The base line was drawn by taking the onset of the right ventricular movement as the point of origin for a horizontal line. Since this is approximately 0.04 sec. after the onset of the QRS, the base line can be arbitrarily drawn at the 0.04-sec. point. Although there is a brief outward movement during early systole due to right ventricular activity (right ventricular movement), the major portion of the trace is below the base line in normal subjects.

clavicular line just beneath the costal margin is designated as K_{FL} and the space from the epigastric area just beneath the xiphoid process of the sternum is designated K_{EX}. The maximum palpable apical thrust or bulge was also recorded when it was located outside the usual designated areas. Traces were taken from the various positions with the recording machine set at the same sensitivity so that the relative amplitudes of the various movements in an individual patient could be compared. Simultaneous records of the Lead II electrocardiogram and the carotid pulse were taken along with the kinetocardiograms. All records were taken during held normal expiration.

Patients

The patients studied in Part I composed two groups: (1) 60 patients with only systemic arterial diastolic hypertension and (2) 55 patients with acquired aortic valvular disease (aortic stenosis and aortic insufficiency). The patients with arterial hypertension had several documented diastolic blood pressures of more than 90 mm. Hg; however, the group was not limited only to those with sustained hypertension. Thus many of the patients had labile hypertension without symptoms or other demonstrable cardiovascular abnormalities. In addition, any patient with evidence (electrocardiographic or clinical) of coronary artery disease was excluded from the hypertensive group. The presence of a peri-infarctional block[4] in the electrocardiogram was not used to exclude any patient and no patient was excluded because of the kinetocardiographic findings. A few hypertensive patients were excluded because the teleoroentgenogram could not be located. Consequently, the series includes a relatively high percentage of patients with labile or benign hypertension. In addition, it represents a rather select group because there was no evidence of any other types of heart disease in these patients. The mean age of these patients as well as that of those with aortic valvular disease was 49 years. Thus, the series contains 115 patients who have the types of

*Table I. Criteria of Sokolow and Lyon for diagnosis of left ventricular hypertrophy**

Standard limb leads
- (a) Voltage R + S_3 = 22 mm. or more
- (b) RS-T_1 depressed 0.5 mm. or more
- (c) T_1 flat, diphasic, or inverted, particularly with (b) and a prominent R wave
- (d) T and T diphasic or inverted in presence of tall R waves and (b)
- (e) T greater than T in presence of left axis deviation with high voltage QRS complex in Leads I and III

Precordial leads
- (a) Voltage of R wave in V or V exceeds 26 mm.
- (b) RS-T segment depressed more than 0.5 mm. in V_4, V_5, or V_6
- (c) Flat, inverted, or diphasic T waves in Leads V through V_6 with normal R waves small S waves, and (b)
- (d) Ventricular activation time in V or V = 0.06 sec. or more

Unipolar limb leads
- (a) RS-T segment depressed more than 0.5 mm. in aV_L or aV_F
- (b) Flat, inverted, or diphasic T wave with R wave of 6 mm. or more in aV_L or aV_F and (a)
- (c) Voltage of R wave in aV_L exceeds 11.0 mm.
- (d) Upright T wave in aV_R

*Only one criterion is used.

tricular thrust was measured from the K_1, K_2, K_3, and K_4 points in all the patients, as well as the maximum amplitude above the base line. From an analysis of traces made from 80 normal subjects (mean age of 49 years) the mean duration on the base line of the maximum left ventricular thrust was 0.045 second with a standard deviation of 0.02. Thus any thrust with a duration of 0.09 second or greater was considered to be abnormal (over 2 standard deviations above the normal mean).

Teleoroentgenographic analysis. Standard 6-foot, posterior-anterior chest films were usually taken within a period of a few days from the time the kinetocardiographic records were made. Only those films from the patients with hypertension were analyzed. Measurements were made according to the methods described by Ungerleider and Gubner.[8] Fig. 4 depicts the measurements used in this study. The frontal areas and the transverse heart diameters were compared to the predicted values based upon the height and weight of the patient.[8] Any frontal area over 110 per cent of the predicted area was considered to be abnormal.[8] Any transverse cardiac diameter over 110 and 115 per cent of that predicted was determined. Ungerleider considered diameters over 110 per cent as possibly abnormal and those over 115 per cent as probably abnormal. The transverse heart thoracic ratio using .5 and greater as abnormal was determined. A clinical impression of heart enlargement was made by simple inspection of the film.

Electrocardiographic analysis. Electrocardiographic analysis was made from the standard 12-lead records of all patients with hypertension and aortic valvular disease. The traces were analyzed for left ventricular hypertrophy according to the Sokolow criteria[10] (listed in Table I). The Grant[5] criterion for left ventricular hypertrophy which was also used is based on voltage. Any total QRS complex (including the R and S waves) in any V lead which measured 40 mm. was considered to indicate left ventricular hypertrophy unless in an individual under 25 years of age. The duration of the intrinsicoid deflection (V_6 lead), the mean frontal QRS vector, and any other abnormality was noted. Left axis deviation was considered to be present when the mean QRS axis was greater than minus 30 degrees.

Results

Tables II through VII present the electrocardiographic, radiographic, and kinetocardiographic findings. Table II presents the electrocardiographic data. Note that the percentage of patients with positive Grant criteria was approximately the same in both groups of patients. In contrast, a higher percentage of patients with aortic valvular lesions had positive Sokolow criteria. Left axis deviation was also more frequent in the patients with aortic valvular disease and 8 of these patients with left axis deviation actually had peri-infarction block,[4] whereas left axis deviation was less common in the patients with arterial hypertension. Significant intrinsicoid prolongation (0.05 second or greater) was more common in the patients with aortic valvular disease than in those with hypertension; however, it is probably a poor

Table III Radiographic analysis

	Impression of enlargement		Cardiothoracic ratio of .50 or more		Cardiothoracic ratio greater than .50		Transverse cardiac diameter greater than 110 per cent of predicted value		Transverse cardiac diameter greater than 115 per cent of predicted value		Frontal area greater than 110 per cent of predicted value	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Class I (36 patients)	13		8		3		14		8		23	
Class II (14 patients)	4		6		6		8		5		9	
Class III (8 patients)	7		7		7		7		7		7	
Class IV (2 patients)	2		2		2		2		2		2	
All patients (60 patients)	28	47	23	38	18	30	31	52	23	37	41	68

Table IV Kinetocardiographic analysis

	Patients with hypertension (60)			Patients with aortic valvular lesions (55)			Combined series (115 patients)		
	Number of patients	Number positive	Per cent	Number of patients	Number positive	Per cent	Number of patients	Number positive	Per cent
Class I	36	26		10	9		46	35	78
Class II	14	12		18	16		32	28	87
Class III	8	8		21	21		29	29	100
Class IV	2	2		6	6		8	8	100
All classes	60	48	80	55	52	95	115	100	87

Table V Comparison of kinetocardiographic and electrocardiographic findings

	Patients with hypertension (60)		Patients with aortic valvular disease (55)		Combined series (115 patients)	
	Number	Per cent	Number	Per cent	Number	Per cent
Abnormal KCG but ECG negative (Grant criteria)	24	40	26	47	50	43
Normal KCG but ECG positive (Grant criteria)	3	5	0	0	3	3
Abnormal KCG but ECG negative (Sokolow criteria)	15	25	8	15	23	20
Normal KCG but ECG abnormal (Sokolow criteria)	3	5	2	4	5	4

Rather intriguingly these relatively simple mechanical measurements serve to specify the first three orders of the electrical characteristics of the double layer. If the dipole moment per unit area of the double layer is k, the total dipole moment of the surface is kA and is directed along the X axis. Since the intersection of the principal axes of inertia coincides with the center of gravity, all first-order (static) moments of the lamina are zero; analogously, all five quadripolar components of the double layer vanish in the frame of reference which we have selected. Five of seven possible octapolar components also vanish, leaving only $a_{xx} = -(3k/2A)(I + I)$, and $a = (k/4A)(I - I)$. Since the a_{yy} component reflects the difference between the maximal and minimal moments of inertia of the lamina, it vanishes in the case of a circular rim or, more generally, in the case of a rim with tetragonal symmetry about the X axis.

The preceding hypothetical example is relatively simple not only because the rim of the double layer is planar but also because a "local" reference system was adopted in which all fifteen components of the first three orders vanish save for one dipolar and two octapolar components. This simplification is permissible, but the description is not complete unless the location and orientation of the local system within the usual anatomic reference coordinates is specified.

The mathematical complexities of the situation increase considerably when the rim of the double layer is nonplanar and/or the components are referred to the anatomic rather than the local coordinate system. These complexities tend to obscure the physical interpretation of double-layer activity as mechanical analogues, but they do not appear to introduce excessive computational difficulties.

The recent electrocardiographic literature contains two closely related proposals for determining the equivalent generator components of the heart from body-surface measurements of potential.[5,6] If the body, including the entire cardiac region, were an electrically homogeneous, linear, and isotropic volume conductor, the equivalent generator components determined from body-surface measurements of potential would be identical to the intrinsic electrocardiographic properties obtained by the type of direct analyses of double layers outlined above. Since it is most unlikely that the body meets these highly idealized conditions, we would anticipate differences between the equivalent and intrinsic multipolar components of the cardiac generator, and these differences should to some extent reflect distortion produced by the actual volume conductor properties of the body as compared to the hypothetically ideal situation. It is conceivable that animal experiments can be designed for the purpose of testing in this way the electrocardiographic distortions produced by the passive electrical properties of a given subject.

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REFERENCES

1. Frank, E.: A comparative analysis of the eccentric double-layer representation of the human heart, Am. Heart J. 16:364, 1953.
2. Brody, D. A.: Limited reliability of precordial electrodes as vectorcardiographic leads, Science 125:352, 1957.
3. Yeh, G. C. K., and Martinek, J.: Multipole representation of an eccentric dipole and an eccentric double layer, Bull. Math. Biophysics 21:33, 1959.
4. Brody, D. A., and Bradshaw, J. C.: The equivalent generator components of uniform double layers, Bull. Math. Biophysics (in press).
5. Geselowitz, D. B.: Multipole representation for an equivalent cardiac generator, Proc. Inst. Radio Engineers 48:75, 1960.
6. Brody, D. A., Bradshaw, J. C., and Evans, J. W.: A theoretical basis for determining heart-lead relationships of the equivalent cardiac multipole, I.R.E. Trans. on Bio-Medical Electronics 8:139, 1961.

Potassium depletion and benzothiadiazine drugs
A source of overconcern?

The diuretic and antihypertensive properties of a variety of benzothiadiazine compounds have been exploited widely in the treatment of edematous states, such as congestive heart failure, diseases embracing the nephrotic syndrome, or cirrhosis of the liver, and in the treatment of hypertensive disease. When these natriuretic agents were first introduced, it was recognized that they lowered the level of serum potassium in some patients and also elevated the plasma carbon-dioxide combining power.[1] An early report dealt with the expected occurrence of digitalis toxicity, apparently the result of chlorothiazide causing loss of potassium.[2] With the development and introduction of each subsequent modification of the benzothiadiazine structure came an assessment of the extent of the urinary excretion of potassium that it would cause. The major advantage stressed for these newer thiazides, other than increased potency, has been the more "favorable" ratio of sodium to potassium that they produce in the urine. Supplementation of the intake of potassium of patients treated with thiazide drugs, either by adding foods

high in potassium content to the diet, or by giving oral potassium salts, has been advocated and frequently utilized. Combinations of the thiazides and potassium salts have been made available commercially to fill this "need" for potassium supplementation.

Is all this concern about potassium depletion valid? It is well known that the concentration of an electrolyte in the serum need not correlate with its total content in the body. The presence of hypokalemia cannot be taken as indubitable evidence of cellular potassium deficiency. Potassium depletion can be accompanied by hypokalemia and also by an extracellular alkalosis, with elevation of the plasma carbon-dioxide combining power, since hydrogen ions enter cells when the cells lose potassium ions. However, the level of serum potassium may also fall without depletion of the total body potassium, as a simple consequence of a metabolic alkalosis which causes the migration of potassium ions into cells. A low serum potassium and a high carbon-dioxide combining power are common to both of these situations. In the case of thiazide administration, which is the primary element? Is it the loss of potassium from the body, or is it the institution of a metabolic alkalosis? This question requires further investigation.

The evaluation of the magnitude of the urinary loss of potassium which results from the use of benzothiadiazine drugs usually has been carried out over a period of time limited to a few days. It is true that the initiation of thiazide therapy does increase the urinary excretion of potassium. This has been stressed so much that the scattered voices which offer evidence that the chronic administration of these *agents need not lead to potassium deficiency* have been virtually overlooked. Talso and Carballo[3] studied 71 patients who were given hydrochlorothiazide or benzydroflumethiazide daily for 28 days. Twenty of these individuals also received supplementary potassium salts. The mean total exchangeable body potassium, determined prior to and at the end *of this course of treatment, irrespective of the* addition or omission of potassium supplementation, showed no significant change. Gifford and associates, although finding a slight reduction in exchangeable body potassium in the first 2 weeks of treatment, observed that the mean value for 5 patients in subsequent weeks actually increased. Likewise, experimental animals show little evidence of potassium deficiency *after the prolonged administration of* thiazides. Delahunt[5] has given large amounts of polythiazide (450 mg. per kilogram of body weight per day) to dogs for 6 months without altering the potassium content of their skeletal muscle. Sones and associates[6] gave chlorothiazide to animals for 5 months without producing a change in total body exchangeable potassium.

It appears that the renal tubules of most patients and experimental animals have the ability to counteract the loss of potassium which may occur in the initial phase of thiazide administration, and can correct any resulting negative balance of potassium in spite of continued daily use of these drugs. The weight of evidence to date supports the view that the hypokalemia which may be present with prolonged thiazide treatment represents a deviation from the normal intracellular-extracellular potassium concentration gradient and not a depletion of the body stores of potassium. It is, therefore, a relatively benign state except for its possible potentiation of digitalis toxicity. The concern about potassium depletion with prolonged administration of benzothiadiazine drugs is unjustified, and the deliberate routine supplementation of the intake of potassium over long periods of time should be abandoned.

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REFERENCES

1. Weller, J. M., Reynolds, E. W., and Judge, R. D.: Clinical evaluation of the diuretic drug chlorothiazide, Univ. of Mich. Med. Bull. 24:44, 1958.
2. Schreiner, G. E., and Bloomer, H. A.: Effect of *chlorothiazide on the edema of cirrhosis, nephrosis, congestive heart failure, and chronic renal* insufficiency, New England J. Med. 257:1016, 1957.
3. Talso, P. J., and Carballo, A. J.: Effects of benzothiadiazines on serum and total body electrolytes, Ann. New York Acad. Sc. 88:822, 1960.
4. Gifford, R. F., Jr., Mattox, V. R., Orvis, A. L., Sones, D. A., and Rosevear, J. W.: Effect of thiazide diuretics on plasma volume, body electrolytes, and excretion of aldosterone in hypertension, Circulation 24:1197, 1961.
5. Delahunt, C. S.: Personal communication.
6. Sones, D. A., Wakim, K. G., Orvis, A. L., and McGuckin, W. F.: *Effects of chlorothiazide on* body electrolytes, Fed. Proc. 19:249, 1960.

Book reviews

CHEMICAL PATHOLOGY OF THE NERVOUS SYSTEM. Proceedings of the Third International Neurochemical Symposium, Strasbourg, 1958 (119 participants). Edited by Jordi Folch-Pi, Harvard Medical School, Boston, and McLean Hospital, Waverley, Mass. Oxford, 1961. Pergamon Press. 20 pages. Price $20.

The format of the symposium and therefore of the book consists of groups of papers in areas of current research and lines of interest in the field of neurochemistry. The outstanding feature of the book, perhaps, is that each of these sections begins with a review of the area by a mature and sophisticated worker in the field, putting the following, frequently avant-garde and speculative research report in perspective.

The various areas covered include inborn metabolic errors, including phenylketonuria, the lipidoses, metachromatic dystrophies, Hartnup and porphyrias, and nutritional metabolic disorders, emphasizing various B vitamins, proteins and recent opinions concerning dietary lipid influences; the biochemistry of copper metabolism, including its binding, transport, storage and influences on the central nervous system, with particular reference to Wilson's disease; a large section in which present recent neuropathologic and histochemical studies which have to do with various aspects of demyelination, including basic studies on protein and lipid metabolism in tracts and peripheral nerves, fluid and electrolyte physiology with reference to distribution and the blood-brain barrier; some chemical influences on central-nervous-system excitability which may play a role in the convulsive disorders, including acid-base changes, glutamic acid metabolism, ammonia and GABA; and five sections on hormones, enzymes and the metabolism of proteins, amino-acids, amines, aromatic compounds, fluid and electrolytes and other current knowledge in the general area of the biochemistry of mental disease.

The contributors are among the world's best known men in the biochemical aspects of the nervous system, and the review articles which begin each section constitute in themselves as good a collection of reference sources as exist under one cover in this young and chaotic field. The kind and degree of solidity of data and conceptual framework, however, varies markedly from area to area, both as a function of the difficulty inherent in the area explored as well as the acceptable level of proof in the scientific climate in each field. For example, there is the work surrounding phenylketonuria as represented by the reports of Armstrong and associates and Knox; versus Mitchell's report on glucose tolerance curves in schizophrenia. The former group represents orderly additions to a systematically growing chemical descriptive characterization of a definite entity; the latter group constitutes another unsystematic, poorly controlled "shotgun" attack on an experimental group as yet not defined. The risk in putting both of these types of research report in the same volume is that the acceptance engendered by the first will transfer in the reader's thinking to the second. However, if this is kept in mind, the unevenness serves as an accurate reflection of the status of neurochemistry today and becomes an interesting feature of this excellent book.

WILLIAM HARVEY: LECTURES ON THE WHOLE OF ANATOMY. An annotated translation of *Prelectiones Anatomiae Universalis*. By C. D. O'Malley, Professor of Medical History, University of California at Los Angeles; F. N. L. Poynter, Head of Wellcome Historical Medical Library, London; and K. F. Russell, Associate Professor of Anatomy, University of Melbourne. Berkeley and Los Angeles, 1961. University of California Press, and London, 1961. Cambridge University Press. 239 pages. 5 illustrations. Price $5.

In *De Motu Cordis* (1628), William Harvey wrote: "On several earlier occasions in my anatomical lectures I revealed my new concept of the heart's movement and function and of the blood's passage round the body. Having now, however, for more than nine years confirmed it in your presence ... I have published it for all to see." The lectures to which he referred were his Lumleian lectures (1616-1618) under the auspices of the Royal College of Physicians. It is evident that the circulation was first considered in a lecture of 1618 rather than in 1616 as has been claimed.

The *Prelectiones* are Harvey's lecture notes, written in Latin with occasional English words and phrases interspersed. A facsimile publication of these notes, with a transcription by Edward Scott, of the British Museum (where the notes are deposited), was issued by the Royal College of Physicians in 1886. The present book is far more than this, and it will accomplish much not only in clarifying the background of *De Motu Cordis* but also in supplying information about Harvey's life and work as well as the treatment of anatomy in his time. It contains a 19-page Introduction by the translator-editors that supplies an enlightening setting for the Lectures. The Lectures themselves are presented in full, with continuity filled in by editorial insertions (in square brackets) and commentary in extensive footnotes. The illustrations are noteworthy: the Rolls Park portrait of Harvey (about 1627) in color; the nineteenth century reconstruction of the Royal College of Physicians building, where the Lectures were delivered; facsimile reproductions of three pages of the Lectures, including the title page—"I begin with Jove / Lectures on the Whole of Anatomy / by me William Harvey / Physician of London / Professor of Anatomy / and Surgery /"

An excerpt from the Introduction is quoted here for the reason that it contains the critical passages relating to the circulation.

It is clear that when he came to writ the notes, he had been making his experiments nd observations on the heart and irculation for a long time. When talking of the systole and diastole of the heart, on folio 77 he writes, Having observed [the motion of the heart] for whole hours at a time, I was unable to discern [these things] easily by sight or touch wherefore I propose that you ought t observe and note Certainly he had already come to definite conclusions about the circulation, for on folio 79v he states dogmatically 'The heart ha ing been extended and contracted just as by a kind of force it propels from the right [ventricle] into the lungs, from the left into the aorta wherefore [occurs] the pulse of the ar teries Again on folio 78v he says Hence the pulse of the artery [is] not from an innate faculty of the valves a according to Galen 13 but by the heart thrusting forth [a is indicated] by autopsy in the live and dead, by reason [and] by experiment with ligatures His view on the origin of the heart beat are clearly set down on folio 77 'The pulse begins at the auricles and progresses to the point herefore as if [there were] two wings WH Nevertheless the heart beats when separated from the uricles and the auricles a aken the somnolent heart These remarks could only follow prolonged observ tions on dissections of living nimals Finally on folio 80v is the conclusive statement, wherefore the beat of the heart produces a perpetual ircular motion of the blood

This book is exactly what one would expect of the distinguished translator-editors It is a scholarly and sensitive presentation of a phase of William Harvey work that had remained in un deserved obscurit u til now

PHYSIOLOGICAL AND PATHOLOGICAL AGING By V Korenchevsky M D edited by Geoffrey H Bourne, D Sc D Phil F Z S Professor and Chairman of Anatomy Emory University Atlanta, Ga New York, 1961 Hafner Publishing Company 514 pages. Price $22 50

This monograph was writt by Dr V Korenchevsky who as born in R sia in 1880 He org nized the Oxford Gerontological Unit in 1945 which he headed til he retired 1952 H t sferred this it to St Bartholomew Hospital in London here he now concentrates on the medical liter ure oncerned w th aging

This book is ompendium of the uthor own experienc nd concept and represents the fruit of his effort It is summary of problems on aging nd concerns review of the literature without u fortunately the uthor ev luation of the literature It cont in summary of many paper from the Russia literature an eport that should be of interest to those who cannot read Russia Again, however the author fail t indicat his opinion of the importance or reliabilit of these reports.

The monograph is divided into chapters which ar concerned ith each of the major systems or physiologic processes, e g aging of nective tissue endocrine glands, heart kidney nervous ystem nd others The hapter entitled "Causes of Ag ng is limited to 2 pages and is almost worthless There are many interesting aspect of ag ng that ould ha e been included in th hapter such a data obtained in the fields of biology other than medicine, including genetics

Unfortunatel this book contains a mass of fact which are not presented critically or in an interesting fashion The monograph is dull but may interest those who ha e read little on the subject of aging It repeats a great deal of the material found in other monogr ph on aging such as Cowdry book A one interested in the aging process should t lea t glance over this book, but if he is alread well informed he will not find many exciting stimulating or new ideas here It is well recognized that the aging process is poorly understood but the great need is for concentr ted clear thinking on the subject, using the data already published onl as a background

CEREBRAL INFARCTION THE ROLE OF STENOSIS OF THE EXTRACRANIAL ARTERIES (Medical Research Council Special Report No. 300). By Peter O Yates nd Edward C Hutchinson, London, 1961 Her M jesty Stationery Office, 95 pages (British Information Service, New York, American agent). Price $2 63

Complete postmortem examination of the cerebrovascular tree from the aorta to the brain was done in 100 persons who died with clinically recognized cerebral ischemia in the Manchester Royal Infirmary during the ears 1955 and 1956 Thirt -one persons who died from know cerebral hemorrhage during the same period were omitted as were persons w th cerebral infarction not associated with degenerative cerebrovascular disease. Patient with symptoms wh h were primaril ps hiatric or w th long histories of remitting illness tended to be excluded since they were not admitted to this hospital Both carotid and both ertebral essels were injected with a radiopaque gelatine mixture and dissection of the essels as carried out indicated by radiogr phs

Cerebral infarction w found in 35 of the 100 subject Very few cases were due to local arterial or lesion w th complet essation of blood flow I onl 23 of the 35 subject wa there significant stenosis or cclu ion of intracranial arteries, but 32 had significant stenosis of the extracranial portions of the cerebral arteries. Thus, in mor than one third of the subject who had cerebral infar tion neither occlusion nor significa t stenosis of the intracranial erebral arteries was found Systemic factor such a h potension nd anemia, ere emphasized Case summaries, utopsy findings, nd maps of the ascular nd cerebral lesions are provided on each patient w th cerebral infarction.

The authors conclude that cerebral infarction usually result from a combination of sy t disease and stenosis of extracranial rter

tracranial arteries or both. Disease of the extracranial arteries was more often associated with cerebral infarction than was disease of the intracranial vessels.

HEMODYNAMICS OF AORTIC AND MITRAL VALVE DISEASE. By Alvin J. Gordon, M.D., Associate Attending Physician and Head of the Cardiac Catheterization Team, The Mt. Sinai Hospital, New York, Consultant for Cardiac Clinical Investigation, Beth El Hospital, Brooklyn, N. Y.; Paul A. Kirschner, M.D., Assistant Attending Surgeon, The Mt. Sinai Hospital, New York, Associate in Surgery, Columbia University, Associate Visiting Surgeon, Chest Service, Bellevue Hospital, New York, Attending Thoracic Surgeon, Veterans Administration Hospital, Bronx, N. Y.; and Howard L. Moscovitz, M.D., Assistant Attending Physician, The Mt. Sinai Hospital, New York. New York, 1961, Grune & Stratton, Inc., 136 pages. Price $5.75.

This monograph of personal experience with transbronchial left heart catheterization reviews briefly the technique and interpretation of pressure pulses in rheumatic mitral and aortic disease. Although transseptal techniques have probably replaced most transbronchial approaches to the left heart, the basic data will be unchanged. The great care taken to secure precision in pulse contours is capped by the elegant electronic derivation of mean pressure gradients (a welcome change from the peak gradients frequently used), which permits greater clarity of physiologic interpretation of other events (murmurs, opening snaps, atrial waves, etc.)

However, clinical interpretations of the valve gradients so obtained are limited by the omission of any determination of cardiac output, or of exercise studies. Selection of candidates (now and in the future) for open or closed mitral and aortic operations requires evaluation of the heart both as a flow and a pressure generator and under conditions of stress.

The chapter on techniques is useful in its detail. Some graphic illustrations of artefacts and poor recording would be helpful. The text is clear and the reproductions are excellent. The book is a useful basic guide to the subjects covered. Angiocardiography is not discussed.

THROMBOSIS AND ANTICOAGULANT THERAPY. Proceedings of a Symposium arranged by Professor P. A. Owren, Professor R. B. Hunter and Dr. W. Walker and held in Queen's College, Dundee, Scotland on Sept. 29 and 30, and Oct. 1, 1960. Edited by W. Walker. Dundee, 1960, D. C. Thomson & Co., Ltd., 106 pages (Williams & Wilkins Company, Baltimore, exclusive U. S. agents). Price $4.25.

This is a summary of papers and discussions on thrombosis and anticoagulant therapy presented at Queen's College, Dundee, Scotland, September 29 through October 1, 1960. The publication was rather slow in appearing but it still is up to date since little new has developed since then anyway. The symposium was attended by many experts in the field under the sponsorship of the University of St. Andrews.

There was nothing especially exciting discussed at the meeting. However, those who do not follow the literature on the subject will find this monograph very useful and interesting. They will find nothing new to support the use of anticoagulants nor any new evidence against their use. This symposium, however, was held before the report of the interesting study from Copenhagen appeared in *Lancet* (August 12, 1961).

The twenty-four papers included in the symposium are well written and well illustrated. The last four pages contain discussions by those present. This is a relatively small but well-written and good symposium on thrombosis and the use of anticoagulants, which should be of interest to clinicians as well as those who are studying the problems of thrombosis and embolism.

Announcement

MEDICAL RESEARCH GRANTS. The Life Insurance Medical Research Fund is now receiving applications for awards to be available July 1, 1963, as follows: *Until Nov. 1, 1962* for grants to institutions in aid of research on cardiovascular problems. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field.

Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 1030 East Lancaster Ave., Rosemont, Pa.

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